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ACUTE INFECTIOUS DISEASES

BY

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DEDICATED TO THE MEMORY OF

DR. WILLIAM M. WELCH

FOR A HALF CENTURY CONNECTED WITH THE PHILADELPHIA HOSPITAL

FOR CONTAGIOUS DISEASES

A SKILLED AND EXPERIENCED PHYSICIAN, AND

ONE OF NATURE'S NOBLEMEN

69444

PREFACE TO THE SECOND EDITION.

This new edition of *Acute Infectious Diseases* has not only been extensively revised, but a number of new chapters on diseases not formerly included have been added. The clinical phases of the chapters on vaccinia, smallpox, chickenpox, scarlet fever, measles, rubella and typhus fever have been in considerable part retained. The chapter on diphtheria has been rewritten and new chapters on the prevention of diphtheria, Vincent's angina, serum anaphylaxis, erysipelas, mumps, whooping cough, cerebrospinal meningitis, the "fourth disease" and erythema infectiosum have been added.

It will be observed that considerable space is allotted to the subject of Vaccination. This is due to the unnecessarily controversial character of this subject. It is a sad commentary upon the intelligence and judicial mindedness of certain elements in the community that it is still necessary to stress the evidence in favor of vaccination.

Considerable space is also given in the chapters on scarlet fever, diphtheria and erysipelas, to the newer tests of susceptibility and immunity and to the specific antitoxin treatment of these diseases.

With the advances in our knowledge and methods of handling acute infectious diseases in recent years, the authors feel there is a distinct place for a record of these achievements and if this latest compilation should merit the endorsement given the earlier volume their labors will have been justified.

The authors wish to acknowledge their indebtedness to the publishers, Messrs. Lea & Febiger, for their uniform courtesy and coöperation.

J. F. S.
J. A. K.

Philadelphia, Pa.

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ACUTE INFECTIOUS DISEASES.

INTRODUCTION.

INFECTION AND IMMUNITY IN RELATION TO THE ACUTE INFECTIOUS DISEASES.

INFECTION IN RELATION TO THE ACUTE INFECTIOUS DISEASES.

Several phases of the subjects of infection and the production of infectious diseases are of special interest in relation to those communicable diseases considered in the present volume. The causes of the following are as yet undiscovered, but are believed to be due to certain active, invisible and transmissible agents commonly designated as "filterable viruses:" Smallpox, vaccinia, chickenpox, measles, rubella (no report on filtration), typhus fever and possibly mumps. Scarlet fever is still regarded by some as belonging to the same group, but the evidence in favor of Streptococcus hemolyticus scarlatinæ (Dick) as the cause of this disease is so strong that the majority accept it as the etiological agent. Erysipelas, diphtheria, whooping cough and epidemic cerebrospinal meningitis are definitely bacterial diseases while in Vincent's angina a spirochete is apparently involved. Typhus fever being a rickettsia disease does not strictly belong to those caused by viruses and it is not unlikely that some of the others will be shown to be caused by small bacteria or protozoa.

Indeed, the filterable viruses exhibit so many differences that a description of them almost demands a separate discussion of each disease. None has been obtained in an absolutely pure state. Even the washed granules of vaccine virus cannot be accepted as virus only, and it is, therefore, impossible to say that virus alone is being filtered rather than virus attached to other substances. The viruses apparently vary considerably in size and none have been successfully measured with acceptable accuracy. About all one may say is that those which pass through tight Chamberland candles are extremely small and yet methods of filtration are crude and inaccurate and failure to pass a filter may be due not so much to size as to the electrical charge of the virus and filter, adsorption of virus by cell detritus, the amount of protein or other substances in the virus emulsion and the temperature, duration, degree of positive or negative pressure and other physico-chemical factors involved in the process.

Furthermore, none of the viruses of the diseases mentioned above have been successfully cultivated artificially or *in vitro* in the absence of living cells. Apparently this is not due to their small size or sensitiveness to adverse conditions but rather because they are obligate parasites reproducing only intracellularly or extracellularly upon living cells and especially young cells. Intracellular cytolytic and cytokinetic changes are of particular interest and in some diseases, like smallpox, cowpox, chickenpox, herpes, etc., may result in the production of inclusion bodies of undoubted importance and significance. Some multiply only in a restricted number of hosts, which accounts for the species specificity of measles, rubella, smallpox, chickenpox, etc., and some show a high degree of "selective tissue localization," as if the case of smallpox, chickenpox, measles and rubella, which usually attack the skin; but the importance of this selective localization is not to be unduly emphasized, since the viruses of several, and especially of cowpox and chickenpox, attack both ectodermal and mesodermal cells.

Insofar as vaccine granules, Guarnieri bodies and other inclusions are concerned, the question of their organized or corpuscular nature has not been satisfactorily settled, since granules which may be seen, held back by filters or thrown down by centrifugation, may not represent virus alone, because as a group they exhibit a remarkable tendency to adsorption by many things with which they come in contact. Indeed, it is impossible at present to say whether the viruses are animate or inanimate, although most investigators regard them as being living microbes.

The possible relationship between the epitheliotropic and neurotropic viruses is engaging considerable attention at present as it would appear that some may be closely related or have a common ancestor. But whether or not viruses can mutate is still a debatable question and engaging considerable attention, although it is by no means a new one, because it has been under discussion since Jenner's time in relation to vaccine virus and smallpox. Certainly when viruses are adapted to alien hosts their characteristics are frequently altered as well as the diseases produced by them, although it is not yet known whether or not it is correct to speak of such as true mutations.

At the present time it is generally believed that the viruses of chickenpox and smallpox are distinct and different, although Hebra regarded them as identical as late as the middle of the nineteenth century; certainly there is a decided difference of opinion in regard to the relation between smallpox and varioloid to alastrim on the one hand and of chickenpox to alastrim on the other. Furthermore, Gildemeister and Herzberg have recently offered experimental evidence to support the view of a close relationship between herpes virus and cowpox virus, and have suggested that one might be a mutant of the other. Since Bokay, in 1909, claimed a relationship between the viruses of chickenpox and herpes zoster a large controversial literature

has developed, as likewise upon the possible interrelationship between the viruses of various kinds of herpes and encephalitis. But it is difficult to believe that the viruses of chickenpox, smallpox and symptomatic herpes possess anything in common, and much of the evidence in favor of their identity based upon cross immunity experiments conducted in the skin of human beings and animals may be due to errors, and especially upon non-specific factors, the result of previous handling or injury which reduces the susceptibility of the skin and cornea to experimental inoculation.

It is apparent, therefore, that many difficulties surround present methods for the study of the viruses and that there are no means for the direct laboratory diagnosis of those virus diseases included in this volume. Fortunately our information regarding the bacterial agents of diphtheria, Vincent's angina, erysipelas, whooping cough and meningitis is much more complete and adequate descriptions of the respective microbes are to be found in textbooks devoted to bacteriology; in the following pages we shall, however, refer to them under the respective diseases, and particularly in the case of diphtheria, Vincent's angina and meningitis, since a simple equipment enables the physician to identify the organisms himself and thereby save considerable time in diagnosis in those localities where laboratories are not readily accessible.

Man himself is the most important single source and reservoir of the etiological agents of the communicable diseases; as stated by Rosenau, man is man's greatest foe in this regard. While the viruses and the pathogenic bacteria exhibit a wide range in resistance to physical and chemical agents, and while some are highly resistant to heat, cold and drying and are sometimes transferred by air and other vehicles, yet spread of infection from man to man by direct contact is of paramount importance and adds greatly to the difficulties of their prevention. Diphtheria may be apparently contracted from infected cats, but otherwise it cannot be accepted as proven that the lower animals are the source of any other of the communicable diseases considered in this volume.

Contact infection is, therefore, of most importance in the transmission of these diseases and assumes the transfer of quite fresh infective material. This may be derived from a patient with the disease or one who has had it and is now an *acute* or *chronic carrier* or one who has never had the disease but has nevertheless become a carrier of the infectious agent. The fact that carriers exist in a large number of the communicable diseases and that laboratory examinations for their detection are of value only in diphtheria, Vincent's angina, whooping cough, meningococcus meningitis and typhoid fever, renders their suppression of great practical difficulty and their cure one of the most important problems in preventive medicine. And adding greatly to these difficulties is the constant presence in our midst of *missed cases* or those mild and atypical infections which are not recognized clini-

cally. True, they usually result in rendering the individuals immune, but in the meantime they go to school, ride in street cars, attend churches and theatres, continue at their usual work, sneeze and cough in our midst and constitute a prolific source of infection of others and the means of creating additional carriers.

Of the three main channels of infection, namely, (1) the respiratory tract, (2) the digestive tract and (3) through the skin, the first mentioned is of most importance. This is certainly true of diphtheria, Vincent's angina, whooping cough, mumps, meningitis and scarlet fever and most likely of smallpox, chickenpox, measles and rubella. *Droplet infection,* or the transmission of microbes and viruses in material from the upper respiratory tract and mouth by sneezing, coughing, kissing and even by ordinary conversation is deservedly commanding a great deal of interest and attention. While it is true that direct contact with such material is most dangerous, yet the possibility of infection by indirect contact with comparatively fresh virus carried into an adjoining room or house, on the hands or clothes of an attendant, on spoons, cups, bed clothing, handkerchiefs, instruments and even books cannot be overlooked or underestimated. In the case of smallpox and scarlet fever even *transmission by fomites* or the spread of infection by articles retaining the virus for a considerable period of time is still to be reckoned with as a possibility. While the evidence of the transmission of the viruses of smallpox, chickenpox and measles by the open air is far from conclusive and has doubtless been greatly overemphasized in the past, yet this means of conveyance and infection of the upper respiratory tract and especially by the dust of dried material as scales and crusts of skin and secretions, still requires careful consideration rather than dogmatic rejection. Furthermore, *milk, water and various articles of food* are to be reckoned with as additional possible carriers of the microbes of some of the communicable diseases, and especially scarlet fever, diphtheria, Vincent's angina, mumps and typhoid fever by reason of direct droplet contamination or the transmission by flies of material from infected individuals, carriers and missed cases. In typhus fever at least it is now known that vermin may be carriers of the virus, but whether or not they may transmit the streptococcus of erysipelas or the viruses of smallpox, measles and other of the communicable diseases considered in the following pages is as yet unknown.

The mere presence of pathogenic microbes and viruses upon the surface of the skin or mucous membranes of an individual constitutes *contamination;* it is not until they have invaded and proliferated in the deeper tissues that *infection* may be said to exist. But it is sometimes impossible to make fine distinctions. A "temporary carrier" is usually one who is merely a contaminated individual, but a chronic carrier is usually one in whom the virus has produced actual infection.

The abnormal state resulting from infection constitutes an infectious disease, but it is impossible to clearly define the term *infectious* and

contagious disease. All diseases caused by living transmissible agents are infectious; only those usually transmitted by direct contact may be properly designated as contagious. Strictly speaking, this latter term is now obsolete even in the case of syphilis, gonorrhea and chancroid, since it is granted that indirect contact with the secretions of these as well as of those communicable diseases dealt with in this volume, may be sources of infection.

Of all the agencies by which pathogenic bacteria produce disease, the soluble or *exogenous toxins* are of most importance. This is certainly true in diphtheria, erysipelas and scarlet fever. Toxins have not as yet been isolated in Vincent's angina, but the pathological tissue changes have all the ear marks of the effects of necrotizing toxins similar to diphtheria toxin. It is possible that *endotoxins* may likewise play a part, but the evidence is not clear. Unquestionably toxins retarding or preventing phagocytosis are very important and especially in diphtheria, Vincent's angina, erysipelas and meningococcus meningitis, but whether these are identical with the toxins mentioned above or constitute separate toxic substances known as *aggressins* cannot be stated. Likewise the absorption of *bacterial proteins* and *toxic exudates* are to be reckoned with and even the possibility of some lesions and symptoms being due to *allergic reactions* to bacterial toxins and proteins, these subjects are discussed in later chapters in more detail in relation to the separate diseases.

Insofar as the viruses are concerned almost nothing at all is known of their pathogenic substances. The clinical course of smallpox, chickenpox, measles and other diseases presumably caused by viruses suggests the production of toxins, but as yet these have not been isolated or studied.

One of the most interesting subjects in relation to the infectious diseases concerns the mechanism of the *period of incubation*, which, beginning at the time of infection and ending with the development of the earliest general symptoms, varies greatly among the acute infectious diseases. In our opinion it represents the time required for: (1) The multiplication of the infecting microbe to pathogenic proportions; (2) the production of toxins; (3) *especially the time required for the latter to unite with or attack certain organs and tissues* for which they may have a selective affinity. No matter how poisonous a bacterial toxin may be, its introduction into the lower animal, even by intravenous injection, is followed by a variable period before symptoms develop which we believe represents the time required for affecting a union with susceptible tissues. Others, as Vaughan and von Pirquet, have expressed the opinion that the period of incubation is the time required for the production of "ferments" and antibodies which, acting upon the infecting microbe and its products, produce poisons responsible for the lesions and symptoms of the disease.

It is evident that the incubation period varies greatly in the different infectious diseases and to some extent in the same disease according

to: (1) The virulence of the infection; (2) susceptibility of the host; (3) to a lesser extent to the site and avenue of infection. Of these factors, that of virulence of the infection is certainly of most importance and in diphtheria, smallpox, scarlet fever and other acute infectious diseases it is common experience to observe marked fluctuations from year to year or at different seasons in the same year, virulence always being highest during epidemics because of enhancement due to rapid transfers of the virus from one susceptible individual to another.

Of all the symptoms of an infectious disease that of *fever* is most constant, although not invariably present. It would appear to be due to a toxic disturbance of temperature regulation and is something more than a mere rise of temperature, commonly designated as "pyrexia" or "hyperthermia," because of the associated tachycardia, increased respirations, diminution of salivary secretion, etc. In other words, it is the most constant general symptom of toxemia along with the effects of the same toxic substances upon the heart, kidneys, blood and other important organs sometimes including the meninges (producing meningismus or acute meningeal congestion). But as in diphtheria, Vincent's angina, erysipelas, smallpox, chickenpox, measles, etc., the distinguishing changes are those occurring in the special organs and especially the mucous membranes and skin, the result of direct infection or the local effects of the selective localization of the viruses for these special organs.

IMMUNITY IN RELATION TO THE ACUTE INFECTIOUS DISEASES.

In no other group of diseases are examples of *natural immunity* so strikingly in evidence as in the acute infectious diseases. In diphtheria and scarlet fever we now know that the Schick and Dick skin tests show that some individuals and especially adults have in their blood enough of the respective antitoxins to afford protection even though such persons may carry virulent diphtheria bacilli and scarlet fever streptococci in their throats and be the means of infecting others. We do not doubt that when the microbes of measles, smallpox, chickenpox, mumps, etc., are isolated that immunological tests may be developed to show that some individuals and especially adults also carry sufficient antibodies in their blood to give a natural immunity to these diseases. Just how and why natural immunity develops in some individuals against diphtheria, scarlet fever and other of the acute infectious diseases is unknown, but the most probable explanation is that antibodies are gradually produced by numerous attacks of the diseases too mild in character to attract attention.

Aside from the presence of these specific antibodies in the blood other non-specific factors may also contribute to the state of natural immunity, such as healthy and intact epithelium, normal secretions, phagocytosis of microbes by leukocytes wandering over the surface of mucous

membranes, the enzymes of epithelial cells, etc., as agents offering effectual resistance to infection unless broken down by unusual virulence or the numerical strength of the invading organisms. Anything tending to break down these defenses in the upper respiratory tract are especially likely to favor infection in measles, scarlet fever, meningococcus meningitis and other of the adult infectious diseases.

As is well known, immunity may be *acquired* in an *active* manner by: (1) An attack of disease and (2) by vaccination. One attack of smallpox, chickenpox, measles, rubella, typhus fever, scarlet fever, whooping cough and mumps usually confers a lasting immunity and for smallpox, diphtheria and possibly scarlet fever we now possess methods of vaccination. One attack of diphtheria does not usually confer an immunity because antitoxins are produced but slowly by human cells and the disease does not ordinarily last long enough at any one time, although repeated attacks gradually result in sufficient antitoxin production to afford protection. Likewise in Vincent's angina and erysipelas one attack does not usually confer a lasting immunity, although a temporary immunity may occur.

But in the virus diseases (smallpox, chickenpox, measles, rubella, typhus fever and mumps) the immunity following an attack is usually lasting; this is rather characteristic of virus infections in general, and has given rise to much speculation regarding the mechanism involved.

According to one view the cells of the individual possess sessile antibodies or the ability to produce them indefinitely, but if this were true it would be necessary to assume that this function is transmissible, since an individual of forty years of age immune to chickenpox contracted at one year of age has surely had many new sets of cells. According to another view the immunity is due to a prolonged persistence of the virus in the body following an attack of the disease and responsible for continued antibody production or a state of resistance to reinfection or superinfection analogous to that believed to occur in a large percentage of uncured syphilitics. Vaccine virus, for example, has been recovered from the lymph nodes of an animal twenty-eight days after inoculation and for twenty-two days after the animal's skin was refractory to reinfection. Likewise the "salivary gland virus" of guinea-pigs has been obtained from immune animals over indefinite periods of time, during which the animals were refractory to superinfection from without. In smallpox, measles, chickenpox, etc., it has been stated that if the lasting immunity were due to a similar persistence of viruses in the tissues that such individuals would be sources of infection to others, but this is not necessarily true.

Another interesting feature concerning immunity to virus diseases is the fact that only immunization or infection with living or active virus affords the maximum of protection to second inoculations. With few exceptions, dead or completely inactivated virus leads to but little or no immunity. Therefore, it appears that an actively acquired resistance is dependent in some way upon an actual infection or vac-

cination with living virus, even though so mild as to give rise to no symptoms. In tuberculosis and syphilis acquired immunity is also dependent upon stimulation by living organisms and this lends confirmation to the view that acquired lasting immunity to diphtheria, mumps, whooping cough, measles, rubella, smallpox, chickenpox, etc., is due to repeated infections so mild that they attract no attention except in the first attack.

The sera of individuals recovering from measles, chickenpox, smallpox and some other of the acute infectious diseases usually contain some demonstrable antibodies affording protection or yielding agglutination, complement-fixation or virucidal reactions *in vitro*, but the degree of immunity enjoyed by the individual is so out of proportion to the presence of these as to lead many observers to believe that the resistance is predominantly a tissue rather than a humoral immunity.

Fortunately immunity to some diseases may be also of a *passive* character or conferred by an injection of antibody serum derived from the lower animals (horses or cattle) actively immunized with the microbes and toxins or from human beings recovering from disease. Diphtheria, tetanus, scarlet fever, erysipelas and antimeningococcus sera are outstanding examples of passive immunization with horse or bovine antisera, while passive immunization against measles and scarlet fever with sera of convalescents are examples of the latter.

Unfortunately the sera of animals naturally refractory to smallpox, measles, chickenpox and other virus diseases do not confer an immunity because lacking in virucidal properties; nor can these properties be developed by repeated injections of active virus. But it is likely that if the viruses of these diseases are successfully cultivated ways and means may be found to produce immune sera artificially by the immunization of the lower animals.

ANAPHYLAXIS IN RELATION TO THE ACUTE INFECTIOUS DISEASES.

The use of horse antisera for the prophylaxis and treatment of diphtheria, scarlet fever, erysipelas, meningitis and other acute infectious diseases has also emphasized the importance of *anaphylaxis*.

This term has been variously defined, but we believe that it is a state of exaggerated and specific hypersensitiveness or allergy to protein agents. The mechanism has not yet been definitely worked out, although it would appear to be due to an antibody in or upon the body cells which are then said to be "sensitized;" upon contact with the exciting agent or antigen some kind of cellular shock reaction occurs responsible for the lesions and symptoms.

The antibody is believed by many to be identical with precipitin, and can be sometimes passively transferred by injecting the serum of the anaphylactic individual into the skin of normal human beings or into guinea-pigs. The "humoral" theory that supposes the union of

antibody and exciting agent or antigen in the blood with the production of a poison called "anaphylatoxin" and responsible for the lesions and symptoms is almost totally lacking in support.

Anaphylaxis to horse serum may be natural or acquired. The former is also known as "atopy," because of the operation of some obscure inheritable factor and is a particularly dangerous type because of the exquisite degree of hypersensitiveness. Such individuals are sometimes rendered asthmatic when in contact with horses and the majority of deaths following injections of diphtheria antitoxin and other immune sera have occurred among them.

Acquired serum anaphylaxis is seldom or never as exquisite or dangerous as the natural type, and occurs in human beings in the form of acute anaphylactic shock characterized by respiratory and cardiac failure or by a train of symptoms and lesions embracing urticaria or other rashes, adenitis, articular pain, fever, etc., so well known as "serum sickness."

Bovine serum is much less likely to sensitize human beings, but so far no method has been discovered for preventing sensitization to horse serum or that of other of the lower animals. Under ordinary circumstances human serum does not produce anaphylaxis in human beings, but when injected intravenously certain "anaphylactoid" symptoms may be produced by intravascular agglutination or hemolysis unless the serum belongs to the same blood group. Furthermore, not all the reactions following the intravenous injection of horse serum into human beings are truly anaphylactic, but are sometimes non-specific anaphylactoid reactions due to intravascular agglutination or some colloidal reaction of obscure nature.

But many physicians have an exaggerated fear of anaphylaxis in the serum prophylaxis and treatment of the acute infectious diseases. Fortunately skin tests are usually of value for the detection of the most dangerous cases, and methods of desensitization are sometimes of value in preparing the less sensitive individuals for injections of immune sera. These will be described and illustrated in a subsequent chapter and especially those dealing with the prophylaxis and treatment of diphtheria and scarlet fever.

CHAPTER I.

VACCINIA.

Synonyms.—Latin, *vaccinia*, or *variolæ vaccinæ* (Jenner); English, *cowpox* or *kinepox;* French, *la vaccine;* German, *Kuhpocken, Impfpocken, Schutzblättern;* Italian, *vaccinia;* Spanish, *vacuna.*

Definition.—Vaccinia is a disease communicable only by inoculation, and is characterized by one or more skin lesions, according to the number of insertions of the specific virus, running through the stages of papulation, vesiculation and pustulation, ending in desiccation and falling of the crusts at the end of the third week. The process is attended by slight febrile disturbance, and when completed confers immunity against smallpox.

History.—When Edward Jenner was pursuing his professional studies with his master at Sodbury, a young country woman, on hearing smallpox mentioned, immediately observed, "I cannot take that disease, for I have had the cowpox." This incident created a deep impression in the mind of the young medical student, and may be said to have been the awakening impulse, which, after years of patient study and experiment, culminated in a discovery which has conferred the greatest benefits upon the human race.

To properly appreciate the life-saving value of Jenner's discovery it is necessary to know something of the fearful mortality of smallpox in the prevaccination days. Admiral Berkeley, chairman of the committee of the House of Commons (in 1802) to investigate the petition of Jenner for a Parliamentary grant, in an eloquent speech said:[1] "The discovery of Dr. Jenner is unquestionably the greatest discovery ever made for the preservation of the human species. It is proved that in these united kingdoms alone 45,000 persons die annually of the smallpox; but throughout the world what is it? Not a second is struck by the hand of time but a victim is sacrificed at the altar of that most horrible of all disorders, the smallpox."

King Frederick William III of Prussia stated in 1803 that 40,000 people succumbed annually to smallpox in his kingdom. The French Minister of the Interior, in reporting on vaccination in 1811, estimated that 150,000 persons died annually in France from smallpox. In Russia smallpox is reported to have destroyed 2,000,000 lives in a single year.[2]

The mathematician, Bernouilli, calculated that not less than 15,000,000 human beings died of smallpox every twenty-five years, which

[1] Quoted by Baron: Life of Jenner.
[2] Woodville: On smallpox. Quoted by Baron.

would give a yearly average of 600,000. Dr. Lettsom estimated that Europe alone claimed 210,000 victims each year. When to this number are added the deaths produced by devastating epidemics in Asia, Africa and America, the aggregate estimate mentioned is seen to be conservative. The early records of the London Asylum for the Indigent Blind showed that three-quarters of the inmates had lost their sight through smallpox.[1] De la Condamine says that this disease destroyed, maimed or disfigured the fourth part of mankind.

Traditions Concerning Cowpox Protection.—The fact that cowpox conferred protection against smallpox appears to have been noticed by dairymen in England as far back as the middle of the eighteenth century. It was observed by these people that when smallpox prevailed those who had been accidentally infected by the matter exuding from certain sores, known as cowpox, which often appeared on the teats and udders of cows, resisted the infection of smallpox.

In 1713 Salger, the author of *De Lue Vaccarum*, called attention to the protective influence of cowpox, and Fewster, a colleague of Sutton, is said to have reported on cowpox as early as 1765 to the Medical Society of London.[2]

It is said that Benjamin Jesty, a Yetminster farmer, was the first person in England to employ cowpox virus for the purpose of protecting against smallpox. In 1774 he vaccinated his wife and children with matter taken from the teats of cows that had the cowpox. In about a week the arms became inflamed and considerable constitutional disturbance was present. The children were later inoculated with smallpox matter without result.

In Germany the protective influence of cowpox was known and practised prior to this date. Jobst Böse, a government official, called attention (*General Conversations of Göttingen*, Pt. 39, May 24, 1769) to the fact that the protection conferred by cowpox against smallpox was recognized by reputable persons. He says: "I am reminded of the not unknown attacks of cowpox which were prevalent in this country, and to which to this day milkmaids are subject. In passing I wish to remark that, in this country, those who have had the cowpox flatter themselves to be entirely free from all danger of getting smallpox, and assert, as I myself, to have heard this same statement made by entirely reliable persons."[3]

In 1791 a school teacher by the name of Platt, who lived in Starkendorf, near Kiel, vaccinated several children of his landlord to protect them against a prevailing epidemic of smallpox. Several years later they escaped smallpox, although intimately exposed to the disease. He was prompted to perform this procedure by the popular belief con-

[1] According to Sir William Aitken, 90 per cent of the cases of blindness met with in bazaars in India are due to same disease.

[2] Hebra: Diseases of the Skin, London translation, 1866, **1**, 271.

[3] Quoted by Kübler: History of Smallpox and Vaccination, Berlin, 1901. Kübler states that the writer of the above commentaries was a man with practical experience in farming.

cerning cowpox protection that prevailed in Saxony and in Holstein. A Holstein farmer, Jensen by name, is also said to have employed prophylactic cowpox inoculation.

In France, a letter from the Protestant pastor of Montpellier, Rebaut-Pommier, to Dr. Pew, in 1781, refers to vaccination.[1]

The same tradition, according to Humboldt, existed in certain parts of Mexico for many years, and similar statements are made concerning this belief in Baluchistan.

An ancient Sanscrit manuscript, called "Sakteya Grantham," is said to have mentioned cowpox as a prophylactic.[2]

But it remained for Jenner to crystallize this half-forgotten tradition into a scientific theory, and then by painstaking study and experiment to establish its truth and prove it to the world.

Referring to the vaccinations performed prior to Jenner's time, Dr. Baron says: "They did not advance the knowledge or the practice of vaccination beyond what casual observation and popular rumor had rendered common in many districts; if indeed they ever took place (which I think more than doubtful) they were quite unknown to Dr. Jenner, and had it not been for his publication they never would have been drawn forth from their obscurity."

Early Practice in England.—Edward Jenner was born in the vicarage at Berkeley, in Gloucestershire, in 1749. He was the third son of Stephen Jenner, rector of Rockhampton and vicar of Berkeley. He exhibited an early taste for natural history, and as a boy interested himself in zoölogy and geology. After his scholastic education was finished he removed to Sodbury, where he became apprenticed to Mr. Ludlow, an eminent surgeon there, to be instructed in surgery and pharmacy. In 1770 he went to London to study medicine under the direction of the celebrated John Hunter, with whom he lived two years.

In 1778 Jenner won the fellowship of the Royal Society, chiefly through his admirable essay, *On the Natural History of the Cuckoo*. Despite his studies in natural history, the tradition concerning cowpox gave him much food for thought and was frequently mentioned by him in conversation with his friends.

After completing his course in medicine and locating in Berkeley, England, where dairy farming was common, Jenner gave close attention to this tradition, and it was not long until he was convinced of its reality.

After having devoted much time and thought to the subject, Jenner determined to inoculate into a human being the vaccine disease, and to test its efficacy by actual experimentation. James Phipps, a lad of eight years, has had his name made historical by having been the first subject to undergo the experiment. The virus used was taken from a vesicle on the hand of a milkmaid named Sarah Nelms, who

[1] Klüber, Jennerian, February 17, 1912; Ring, John: Treatise on Cowpox, 1801, p. 1021.

[2] Oliver, George: Plain Facts About Vaccination, 1871, p. 19.

had been accidentally infected while milking a cow. This vaccination was performed, May 14, 1796, and was the beginning of Jenner's work which has made his name immortal. On the second day of July following Jenner proceeded to test the efficacy of this vaccination by inoculating the lad with smallpox matter taken from a patient suffering from that disease. The result was negative. At various intervals afterward, until this lad grew to be a man, he was inoculated with smallpox matter, in all as often as twenty times, and each time was found to be immune to that disease. It is no wonder, then, that Jenner arrived at the conclusion in his treatise on vaccinia that a single vaccination confers permanent immunity from smallpox.

It was not until Jenner felt perfectly secure of his position that he ventured to detail his experiments and formulate his conclusions in a paper. This paper was prepared in 1797. It was Jenner's intention that this should first appear in the *Transactions of the Royal Society*, but this design was abandoned and the work subsequently appeared as an independent publication. In 1798 he published it as a modest brochure, entitled *An Inquiry into the Causes and Effects of the Variolæ Vaccinæ, a Disease Discovered in Some of the Western Counties of England, Particularly Gloucestershire, and Known by the Name of Cowpox.*

This publication at once attracted great attention from the medical profession in London and throughout England. Like all innovations, the "new inoculation" was viewed favorably by some, with distrust and skepticism by others, while a few resolved to test it for themselves.

Among the first in London to make use of the new discovery were Dr. George Pearson, physician to St. George's Hospital, and Dr. William Woodville, physician to the Smallpox and Inoculation Hospital. But the early work of these gentlemen tended to impair confidence in vaccination because of the accidental contamination of the vaccine virus with smallpox material.

When the news of Jenner's discovery had reached the various civilized countries of the world he became literally overwhelmed with correspondence. This grew to such immense proportions that he was forced to neglect his private work. He was, as he said, for many years the vaccine clerk of the world. All this involved a large expenditure of money, while he was reaping no substantial reward from his discovery. Finding that his small fortune was rapidly diminishing, some of his friends advised him to make application to the British Parliament for an honorarium.

After the proposition to remunerate Jenner had been before Parliament a long time, and had been fully considered by a committee, a grant of £10,000 was voted him. This occured in 1802. But considerable time elapsed before the money was paid, and its collection cost Jenner £1000. Feeling that this grant was very much too small for a great country like England to bestow upon her greatest benefactor, Jenner's friends petitioned Parliament again in 1807 for a

second grant of £20,000. By this time the value of his discovery was better known and more generally appreciated, so that this grant was allowed with much less opposition than the first; it was provided in the act that the amount should be promptly paid without any expense to the grantee.

Jenner labored incessantly to disseminate throughout the world a correct knowledge of this life-saving agent. In 1799 he published *Further Observation on the Variolæ Vaccinæ, or Cowpox,* in which he carefully pointed out the difference between genuine and spurious cowpox.

It was not long before the merit of Jenner's discovery was universally admitted. In many instances the crowned heads of Europe set a good example by promptly accepting vaccination, and very soon arrangements were made to confer its blessings on the peasantry without cost. Honors were freely conferred upon Jenner from every European country, and he was regarded as the greatest benefactor the world had ever known. A letter from him served as the best passport one could have in travelling through foreign countries in time of war. As showing how highly he was esteemed, it is said that during the Napoleonic War two British subjects were held as prisoners by Napoleon, and that Jenner was importuned to write a letter requesting their release. The letter was read to Napoleon by Josephine, and when she mentioned the name of the writer, Napoleon exclaimed: "Jenner! Oh, we can refuse nothing to that man." And the prisoners were promply released and permitted to return to England.

The Dowager Empress of Russia, Maria, wrote Jenner a most complimentary letter and accompanied it with a gift of a ring set in diamonds. In honor of the discovery she gave the name of "Vaccinoff" to the first child vaccinated in the Russian Empire, and settled an annuity on it for life.

In 1821 Jenner was further honored by being appointed physician extraordinary to the King of Great Britain.

The fame of Jenner spread throughout the entire civilized world. The most distinguished scientific bodies vied with each other in conferring honors upon him. From 1801 to 1822 Jenner received no less than twenty-eight diplomas from institutions of learning and scientific societies in every country of Europe and in the United States and Canada. Complimentary addresses were sent to him by public bodies and eminent individuals in every part of the world. In 1803 the corporation of London voted Jenner the freedom of the city, which was presented to him in a golden box. In the several succeeding years Dublin, Edinburgh, Liverpool and Glasgow conferred similar honors upon the illustrious, but modest physician.

Within a period of six years eight medals were struck in Europe in honor of the great discovery. In 1804 one of the most beautiful of the Napoleonic series of medals appeared, commemorative of the emperor's estimate of the value of vaccination.

Jenner died of an apoplectic attack on January 26, 1923. Twelve days before he expired he wrote: "*My opinion of vaccination is precisely as it was when I first promulgated the discovery. It is not in the least strengthened by any event that has happened, for it could gain no strength; it is not in the least weakened, for if the failures you speak of had not happened the truth of my assertions respecting those coincidences which occasioned them would not have been made out.*"

The Early Practice of Vaccination in Other Countries.—FRANCE.—The practice of vaccination had traversed the wide expanse of the Atlantic and was in vogue in America before it was employed in the French capital. Valentin and Desoteux were the first French writers to call attention to the subject. Colladon, of Geneva, visited Paris on his return from England, and vaccinated some patients at the Salpétrière. These vaccinations were unsuccessful. The failures were however, unable to stem the growing tide of popularity of the new inoculation. Dr. Aubert was sent to London in 1800, as the representative of the National Institute and School of Medicine, to obtain all possible information and to secure virus. In the meantime, Liancourt commenced a subscription to establish a vaccine institute, and secured the moral and financial support of Lucien Bonaparte, then Secretary of the Interior. In January, 1800, Dr. Jenner's publication was translated into French by Count de la Roque. Five years later Napoleon demonstrated his confidence in vaccination by ordering all soldiers to be vaccinated who had not passed through smallpox.

SPAIN.—In the year 1800 the practice of vaccination reached Spain, through the efforts of Don Francesco Piguilem, who performed the first successful vaccinations in December of that year. Dr. Jenner's "Inquiry" was translated into Spanish in the early part of 1801. Spanish colonies were supplied with lymph through repeated arm-to-arm vaccinations of children on board ships.

INDIA.—Jenner endeavored to spread the benefits of his discovery into Asia and Africa. He sent his publications and large supplies of virus to India, but the boat carrying these was lost at sea. He was about to start a subscription to send another vessel when he received the tidings that Dr. De Carro, who had introduced vaccination into Vienna, had forwarded vaccine matter from that city to Constantinople and thence to Bombay. In a short time from 2000 to 3000 children were vaccinated in the latter city.

ITALY.—To Dr. Louis Sacco, of Milan, belongs the credit of having been one of the earliest and most successful disciples of Jenner. In 1801 he introduced vaccination into the Cisalpine Republic, which gave authoritative sanction to the practice and made him Director of Vaccination. Sacco labored with unwearied activity, and in a few years performed over 20,000 vaccinations. In many of these the virus was obtained from an animal with natural cowpox, which was discovered in Lombardy after a prolonged search.

Sacco was a warm admirer of Jenner, and the esteem was recipro-

cated by the latter. A letter written to Jenner in 1801 by Sacco begins thus: "It is to the genius of medicine, to the favorite child of Nature, that I have the honor to write. The name of Jenner will be always beloved by all posterity," etc.

Austria.—The zeal and energy of Dr. De Carro were largely responsible for the early employment of vaccination in Vienna (1799). Besides being influential in disseminating this practice throughout other countries, De Carro interested his friend Count de Salm, who worked for the cause with the greatest energy and activity. This philanthropic nobleman distributed virus and literature gratuitously, and held out rewards to physicians who performed the greatest number of vaccinations. The good people of Brunn erected a temple which was dedicated to Jenner, and in which they annually held a festival to celebrate his natal day.

Germany.—Jenner sent virus to Prussia which was used to vaccinate the Princess Louisa. The admirable example set by the royal family excited a general confidence in the measure and led to its widespread employment. The king actively interested himself in vaccination, and founded a Royal Inoculation Institute in Berlin under the direction of Dr. Bremer. The latter collected funds to have medals struck commemorative of Jenner's discovery. These were given to the parents of vaccinated children when the latter were brought back for inspection on the seventh day. In 1799 Ballhorn and Stromeyer introduced vaccination into Hanover. The former gentleman translated Jenner's work into the German language. To Bavaria is due the distinction of being the first country to enforce compulsory vaccination (1807).

Switzerland.—Vaccine matter was carried by Dr. Peschier to Geneva from Vienna, where he had studied the process under De Carro. The physician who labored most earnestly in Geneva in the cause of vaccination was Odier, who in 1801 wrote a memoir on the subject of cowpox.

Russia.—In 1801 some of De Carro's ivory point and threads were sent from Breslau to Moscow, where the Russian court was assembled. Both Emperor Alexander and the Dowager Empress evinced a keen interest in vaccination and energetically promoted its employment.

Denmark.—In the summer of 1801 Jenner gave some vaccine matter to Dr. Marcet for use in Copenhagen. His majesty, the King of Denmark, manifested a "personal solicitude for the welfare of his people," and, after receiving the report of an investigating commission on the subject, approved of all of the regulations suggested. The committee, of which Professor Winslow was a distinguished and active member, recommended legislation, the enaction of which stamped out smallpox in Denmark for almost twenty years.

America.—The introduction of vaccination into this country marks an epoch of great importance. Smallpox had been present here almost from our earliest history. During the eighteenth century it was particularly rife in certain parts of the United States. The New England

States attempted to prevent, by various legislative enactments, the introduction of smallpox into that section of the country. In some of these states variolous inoculation—a measure commonly practised during the middle and latter part of the eighteenth century was prohibited by law. In order that the practice of inoculation should be conducted with as little risk as possible of the disease spreading by the natural transmission of infection, Dr. Benjamin Waterhouse, the first professor of theory and practice of medicine in Harvard College, published important rules and regulations governing the practice of the smallpox inoculation. Having thus been engaged in considering measures for restricting the spread of smallpox, it is not surprising that this physician should have been the first to urge upon the citizens of Boston the acceptance of Jenner's discovery.

Early in the year 1799 Waterhouse received from Lettsom, of England a copy of Jenner's brochure of *Variolæ Vaccinæ*, and he became at once deeply impressed by the new and wonderful facts it contained.

After Waterhouse had collected together a mass of evidence in support of the efficacy of vaccination, "too great," as he says, "to be resisted by any mind not perverted by prejudice," he began to seek the treasure. After several fruitless attempts to obtain the virus in an active state from England, he at length received some from Dr. Haygarth, of Bath, by a short passage from Bristol, and with it vaccinated successfully some of the younger members of his own family. This virus was received the latter part of June, 1800, and on July 8 he vaccinated one of his sons, Daniel Oliver Waterhouse, aged five years. So far as existing records show, this boy was the first person vaccinated in America.

Dr. Aspinwall, who was the physician in charge of the Smallpox Hospital, at once signified his willingness to assist in the experiment, and about two months after the vaccination of Waterhouse's children they were sent to the hospital and not only freely exposed to the infection of smallpox, but also inoculated with fresh matter taken from a patient. Finding the children resisted the disease absolutely when subjected to this most crucial test, Waterhouse exclaimed: "One fact in such cases is worth a thousand arguments."

Early in the spring of 1801 Waterhouse received fresh supplies of virus from Jenner, Lettsom, and other friends in England. With additional information and fresh virus he began vaccinating again, and was rejoiced to find that the vaccine disease presented all the characteristics of the first case in his own family. He was now anxious that the benefits of vaccination should be diffused throughout this entire country. As he had received some months before a letter from Thomas Jefferson, President of the United States, in which this high dignitary manifested considerable interest in the subject, Waterhouse concluded that if the Chief Magistrate of the nation could be induced to take hold of the matter, vaccination would be introduced into the South more speedily

and safely than by any other agency. The letter of the President contained not only an acknowledgment of the receipt of Waterhouse's pamphlet on the subject of cowpox, but a very complimentary reference to his humane work. The letter read as follows:

WASHINGTON, December 25, 1800.

SIR: I received last night and I have read with great satisfaction your pamphlet on the subject of kinepock, and I pray you to accept my thanks for the communication of it.

I had before attended to your publications on the subject in the newspapers and took much interest in the experiments you were making. Every friend of humanity must look with pleasure upon this discovery by which one evil more is withdrawn from the condition of man, and must contemplate the possibility that new improvements and discoveries may still more and more lessen the catalogue of evils. In this line of proceeding you deserve well of your country; and I pray you accept my portion of the tribute due you, and assurance of high consideration and respect, with which I am, sir,

Your most obedient, humble servant,

DR. WATERHOUSE, Cambridge. THOMAS JEFFERSON.

Waterhouse had the satisfaction of knowing that the virus which first proved effective in New York City came from him. Vaccine virus first reached Philadelphia in an effective state, November 9, 1801. It was forwarded by the President, Thomas Jefferson, through Mr. John Vaughan, to Dr. John Redman Coxe, and was accompanied by a personal letter from the President, full of valuable instruction as to its proper use. The first person who is said to have been successfully vaccinated in Philadelphia was Dr. Coxe himself.

Soon after Jenner's brochure was published there appeared in almost every civilized country in the world one or more supporters of the new discovery who adhered more faithfully than others to the teachings of the master, and consequently achieved distinction in this new field of beneficient work.

Waterhouse, of Boston, Sacco, of Milan, and De Carro, of Vienna, were the most faithful followers of Jenner. Of his many disciples, Waterhouse was probably the ablest and worthiest. It is, perhaps, not too much to say he was so regarded by the great benefactor himself. The published letters of Jenner clearly indicate his high esteem of this disciple. He well deserved the confidence of the master, for, single handed and alone, in his own city, he faithfully and earnestly defended and vindicated vaccination against the ridicule of the profession and the prejudice of the public for seven years, or until conviction became too strong for argument, and theoretical objections were forced to give way to stubborn facts. So earnestly, constantly and successfully did Waterhouse devote his time and talent to the dissemination of vaccination in this country, and always so precisely in accordance with the teachings of Jenner, that he received the complimentary title of the "Jenner of America;" not, as might be supposed, by favor of the medical profession of his own country, but by the unanimous voice of the London Medical Society.

THE HYGIENE OF VACCINATION.

In order that a vaccination may pursue a perfect course and remain free of subsequent complications it is important that certain precautions be observed. These may be classified as follows: (1) Care as to purity of the vaccine virus; (2) condition of the vaccinée; (3) asepsis during insertion of the virus; (4) subsequent protection of the vaccine lesion.

Purity and Potency of Vaccine Virus.—Vaccine virus may be of bovine origin. Since 1899 the use of calf lymph has become generally and, indeed, almost universally adopted since acceptable methods have been developed for maintaining a supply of lymph at once pure and efficient. The German government in 1884[1] passed a law that vaccinations and revaccinations in Germany be performed exclusively with animal vaccine.

At the present day glycerinated calf lymph is practically universally employed. This material is employed in two different forms—as a lymph and as a vesicle pulp. Lymph, which is the clear fluid contents of well-developed vaccine vesicles, has been in use a long time. Pulp, which is a combination of the lymph and the interior epithelial structure of the pock, has more recently come into favor, and is at the present time regarded as possessing greater vaccinal activity than the clear fluid. Vaccine lymph is used either in the dry form upon strips of ivory or celluloid (so-called "dry points") or in sealed capillary tubes if the form of a glycerin emulsion.

Great care is exercised in the manufacture of calf virus and elaborate precautions are taken to avoid any chance of sepsis. The addition of glycerin destroys the ordinary bacteria and every batch is subjected to rigorous cultural and animal inoculation tests for tetanus bacilli and spores and other organisms by the manufacturer and the Hygiene Laboratory of the United States Public Health Service before being released for the vaccination of human beings. Various other methods have been tried for the production of germ-free virus and especially by the inoculation of the testes of the bull and rabbit or brain of the latter by Noguchi, Levaditi and others, but experience has shown that these viruses are generally too weak in vaccinal activity for practical purposes.

Various methods are employed for testing the potency of virus. According to the United States Public Health Service,[2] a fair test that the vaccine is of full potency is that when properly applied it give 100 per cent of vaccinias (typical "takes") in every application on a least 100 previously unvaccinated individuals. A more practical test is that it should give more than 50 per cent of vaccinoid reactions in persons who have been vaccinated or have had smallpox over ten years previously, and immunity reactions or typical vaccinias in the

[1] Resolution of the Imperial Vaccine Commission of 1884; approval of the resolution by the Bundesrath, 1885.

[2] Pub. Health Repts., 1927, **42**, 228.

remainder; a much smaller number of individual vaccinations will give a good idea of the potency of a batch of vaccine by this test.

Various methods are also used for measuring potency by animal tests, and the Smallpox and Vaccination Commission of the Health Committee of the League of Nations meeting in Berlin in January, 1927, stated that vaccine lymph may be considered as potent if, at the time of use, it produces the following results:

Method of Calmette-Guerin.—One cubic centimeter of vaccine lymph diluted to 1 to 1000, when distributed over the entire prepared area of the rabbit's skin immediately after it has been shaved, washed and dried, should produce an eruption of isolated vesicles numbering from 3 to 4 per square centimeter of the field inoculated. The results should be recorded on the fourth day after inoculation.

Method of Gins.—Seventy-two hours after the guinea-pig's cornea is scarified and infected with a 1 to 1000 dilution of the vaccine lymph, a marked opacity of the entire cornea (keratitis vacciniæ) should be apparent to the naked eye.

Method of Groth.—Seventy-two hours after intradermal injection into the depilated skin of the back of the rabbit, 0.1 cc. of vaccine lymph diluted 1 to 1000 should produce an area of local infiltration and redness which can be clearly seen and recognized by palpation.

Sobernheim's Method.—The injection of the vaccine lymph diluted to 1 to 1000, according to the method described above, into the skin of the rabbit, should, once the traumatism has passed away, begin to produce a specific reaction after three days. This reaction shows itself at first as redness and a papilliform infiltration at isolated points along the lines of incision. Papules (of the size of a pea) and in some cases pustules are also formed. Sometimes papules and pustules also appear between the lines of incision. The specific eruption shows crusts and scabs. If the vaccine lymph is more virulent a papular infiltration spreads slightly along the line of incision instead of circumscribed papules.

Force and Leake[1] have recently reviewed the literature on potency tests, and have described a test based on Belin's modification of the method of Calmette and Guérin. They also suggest the following criterion of potency: A smallpox vaccine of high potency, when diluted to 1 to 1000, should produce a confluent eruption in from 10 to 100 per cent of the vaccinated area on the back of a rabbit, and when diluted 1 to 3000 the decrease in confluence should not be over 20 per cent. In all previously unvaccinated human subjects such a vaccine should produce successful vaccination.

The colder smallpox vaccine is kept the better; well below freezing is advisable. Ice-box refrigeration is not cold enough for this purpose. Smallpox vaccine cannot be injured by freezing, as can sera and other vaccines. Even a whole day out of cold storage, in addition to the

[1] Hyg. Lab. Bull., 1927, No. 149.

necessary transportation from the manufacturing laboratory, may produce detectable deterioration in potency. Smallpox vaccine which has been out of cold storage, so that it gives only about 80 or 90 per cent of successful vaccinations on previously unvaccinated individuals, may be satisfactory in ordinary outbreaks of smallpox or in routine vaccinations, but in the presence of severe smallpox, or when reactions of immunity are to be observed, the vaccine should be obtained direct from the manufacturer and kept below freezing. In an electric refrigerator the smallpox vaccine should be kept in an ice-making compartment. Next best to storage below freezing is placing the vaccine in a metal or glass container which presses against a block of ice. If a vacuum bottle is used for transporting smallpox vaccine the inside of the bottle should be packed with ice around the vaccine. Fortunately, severe outbreaks of smallpox tend to occur in cool weather, and cause sufficient demand for the vaccine, so that it is shipped very directly from the manufacturing laboratories and is used rapidly. In the presence of severe smallpox, when there is uncertainly as to the potency of the vaccine, vaccination should be performed at more than one site, at least 1 inch apart, preferably with vaccine from different sources. Batches differ in their keeping qualities, but in recent years smallpox vaccine has with uniformity been found to be satisfactory as it leaves the manufacturer.

Condition of the Vaccinée.—There is nothing in the condition of a child that constitutes a sufficient contraindication to the performance of vaccination, if there be liability of exposure to the infection of smallpox. When smallpox is not prevalent it is proper for physicians to exercise discretion in choosing the time for the vaccination of an infant. There being no urgency, the medical adviser may wait until the child has reached a favorable age and is in good condition for the reception of the vaccine disease.

Age of Child.—In order that the proper protection against smallpox may be granted to infants it is advisable that they should be vaccinated during the first year of life. The vaccination laws of Germany require that every child be subjected to this measure before the expiration of the first year of life, unless it is contraindicated by reason of poor health. The age which is generally considered most appropriate is between *four and six months,* for at this period the child has not yet begun to be disturbed by the process of dentition. If there be danger of smallpox there is no reason to delay because of the tender age of the child. We have on a number of occasions vaccinated infants immediately upon their appearance into the world, and we do not recall any bad effects that have resulted from such early vaccinations. Indeed, we have been impressed with the very slight degree of constitutional disturbances that has attended such vaccinations. Where, however, no haste is necessary we deem it well to wait for several months until the child becomes stronger and more accustomed to its mundane environment.

Health of the Child.—It is best to delay the performance of vaccination (provided smallpox be not prevalent) if the child is poorly nourished, or suffering from diarrhea or vomiting, scrofulous glands, eczema, etc., or if the infant has been recently weaned or placed upon some new food. In general terms it may be said that when smallpox is not prevalent the physician may select such time for the vaccination of an infant as may find it in the best physical condition.

Contraindications to Vaccination.—As stated by the Public Health Service, skin diseases, particularly eczema, are the only conditions which will justify school attendance and at the same time be contraindications to routine vaccination. This is on account of the danger of diffuse vaccinia from carrying the vaccine into the open lesions of the skin disease, or the danger of contaminating the vaccination site if the skin lesions are purulent. Patients with such diseases as tuberculosis are in no wise harmed by properly performed vaccination. Acute infectious diseases may cause a vaccination "take" to be delayed or atypical, but are not in themselves contraindications in case of possible exposure to smallpox. There is a curious relation in leprosy which tends to cause the lighting up of leprous lesions during the course of the vaccination, but which promote more rapid healing thereafter. Serious lymphomatous diseases, including lymphatic leukemia, may be made worse by vaccination.

TECHNIQUE OF VACCINATION.

Vaccination being in a sense a surgical procedure, its performance must be guarded by those precautions of asepsis which at the present time apply to all vesical manipulations. Laboratory studies and practical experience have both shown that even in the most trivial of all surgical procedures—the introduction of a hypodermic needle into the skin—certain precautions as to bacterial cleanliness are necessary. Many years ago, before the days of bacteriology, this truth was not known, and consequently proper care was not, as a rule, observed either in surgery or in the practice of vaccination.

In order that all wound infections may be avoided it is advisable that the arm of the vaccinée, the instrument to be employed and the hands of the vaccinator be perfectly clean. Furthermore, the vaccine vesicle should be so protected as to prevent subsequent infection at the site of vaccination.

Some difference of opinion exists as to the thoroughness with which disinfection of the proposed vaccination area should be carried out. Some writers urge such a preparation of the skin as is practised prior to an ordinary surgical operation. Others believe that the use of strong antiseptics is to be avoided inasmuch as they may destroy the activity of the vaccine material when placed upon the skin.

The vaccination area, usually the arm, should be thoroughly washed with soap and hot water, some friction being used so as to distend

the cutaneous capillaries. Personally, we prefer to follow this cleansing with the application of alcohol, although in cleanly persons this is perhaps not necessary. The arm is then to be dried with sterile absorbent cotton, or, when this is not available, a perfectly clean towel. Indeed, single cleansing with alcohol or acetone (preferred) alone is usually sufficient. The instrument used should be previously disinfected by boiling, immersion in an antiseptic solution, or thorough cleansing with soap and water or alcohol. It is perhaps better to employ a needle for the purpose, inasmuch as a new and clean one can be used for each vaccination.

The insertion of the deltoid muscle is the site usually selected for the introduction of the virus.

Leg vaccinations are exposed to more moisture and to more contamination from street dust than vaccinations at the region of the deltoid insertion. On account of blood stasis, primary leg vaccinations in adults are often accompanied by a purplish discoloration, and may result in a large, slowly healing ulceration; they usually cause temporary disability.

If a scratch method is employed it is *important that the abrasion be not too deep.* The drawing of blood is to be avoided, inasmuch as it may float away the lymph and prevent absorption; it is further claimed that the deep scarification is more likely to be followed by an excessive degree of inflammation. It is not desirable to abrade deeper than is necessary to see the little reddish points which represent the loops of the papillary bloodvessels.

Any method is satisfactory which insures that the vaccine is deposited in the deeper layers of the epidermis with no more injury and over no greater an area than $\frac{1}{8}$ inch or 3 mm. in any direction and which avoids poulticing the developing vaccination. With any scarification method, to secure the maximum number of "takes" possible with the virus used, the vaccine should be rubbed in with the side of the scarifier or with a sterile toothpick for at least fifteen seconds.

Several methods may be employed for vaccination as follows:

The Scratch Method.—A drop of the virus is placed on the skin. If supplied in a capillary tube it should be pushed through the small rubber bulb which accompanies it, wiped with alcohol, and the end broken off; the other end is broken off in the bulb and the contents expelled (Fig. 1).

The under surface of the arm is grasped with the operator's left hand so as to stretch the skin where the virus has been placed; with a sterile needle or other suitable instrument a scratch not deep enough to draw blood is made through the drop of virus, parallel with the humerus and about $\frac{1}{4}$ inch long (Fig. 2).

The virus is then gently rubbed in with the side of the needle or other smooth, sterile instrument, as a toothpick (Fig. 3). Some blood-tinged serum may ooze through the virus, but this should not be sufficient to wash the virus out of the wound.

FIG. 1.—Applying a drop of virus to the skin. (Kolmer: Infection, Immunity and Biologic Therapy, W. B. Saunders Company.)

FIG. 2.—Abrading the skin with a needle through the virus. (Kolmer: Infection, Immunity and Biologic Therapy, W. B. Saunders Company.)

The virus should be allowed to dry on the abrasion for at least fifteen minutes.

The vaccinal wound should now be covered with a square of sterile gauze fastened to the skin by adhesive strips (Fig. 4); if other shields

FIG. 3.—Rubbing in the virus followed by exposure for fifteen minutes for drying. (Kolmer: Infection, Immunity and Biologic Therapy, W. B. Saunders Company.)

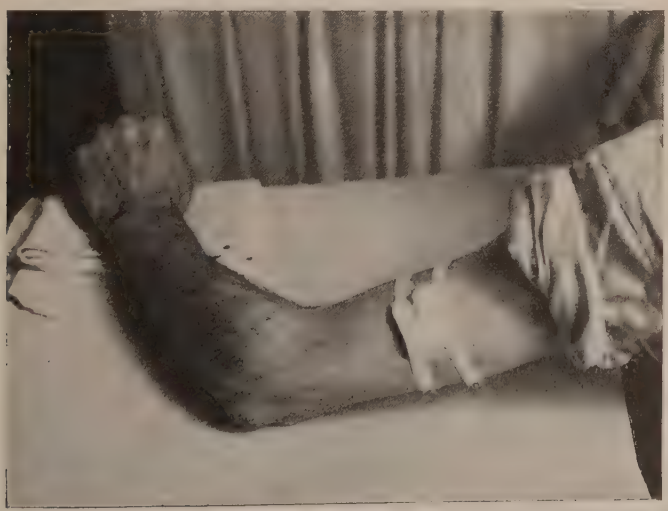


FIG. 4.—Dressing the wound. (Kolmer: Infection, Immunity and Biologic Therapy, W. B. Saunders Company.)

are employed care must be exercised in order that the wound shall be properly protected against contamination without maceration of the skin.

Cross-scarification, which is forbidden in Germany, favors the growth of anaërobic bacteria under the crust that forms on the surface of the abrasion where the resistance is lowered by the action of the virus. The circular scarification gives more control over the dosage, and there is no tendency to the development of excessively sore areas.

Usually one *inoculation* of the virus is sufficient, but in time of a threatened epidemic two or more inoculations are made at the same time, not only to insure a successful result, but rapidly to immunize the patient. It would appear that the degree of immunity bears some relation to the number or size of the vaccination lesions, and this can readily be understood if the infection is local and the body cells are stimulated by a diffusible toxin. If, however, the vaccination lesion is but the point of entry of what becomes a general infection, then a small lesion should suffice. This point has not been definitely settled, but statistics tend to show that persons vaccinated in two or more areas develop an immunity more quickly and that this immunity is more lasting.

Multiple Pressure or Prick Method.—According to the Public Health Service this is the best method and is described as follows: "It consists of a shallow, tangential pricking of the cleansed, but not irritated, skin with a needle, through a drop of smallpox vaccine, covering an area not greater than $\frac{1}{8}$ inch (3 mm.) in diameter. This gives little chance of accidental infection and the eruption is typical. Acetone has been found satisfactory for cleansing the skin. It is somewhat more efficacious and rapidly drying than alcohol. The needle, which should be new, sharp and sterile, is not thrust into the skin, but is held quite parallel or tangential to it, with the forefinger and middle finger of the right hand above the needle and the thumb below, the needle pointing to the operator's left. The needle should be crosswise of the arm so that the thumb of the operator is not impeded by hitting the skin (Fig. 5). The side of the needle point is then pressed firmly and rapidly into the drop about thirty times within five seconds, the needle being lifted clear of the skin each time (Fig. 6). This rapid to-and-fro motion of lifting the needle and pressing it against the skin should be quite perpendicular to the skin and needle and not in the direction of the needle. In this way the elasticity of the skin will pull a fraction of an inch of the epidermis over the point of the needle at each pressure, so that the vaccine is carried into the deeper epithelium (cuboidal, prickle-cell layer), where multiplication takes place most easily. If the skin has not been unduly rubbed in cleansing, and if the motion is entirely perpendicular to the needle, no signs of bleeding will occur and all evidence of the punctures will fade out in less than six hours. Immediately after the punctures have been made the remaining vaccine is wiped off the skin with sterile gauze and

the sleeve pulled down, the whole operation of puncturing and wiping taking less than ten seconds. With strong vaccine a single pressure not infrequently gives a 'take.' Only six pricks or punctures were formerly advocated; comparative tests showed this to be inferior to the scratch method in percentage of "takes." By the use of thirty pricks this difficulty has been overcome, and the percentage of "takes" is as high as with any other safe method. For primary vaccinations, where the mildest possible 'take' is desired, and where other attempts with highly potent vaccine will be made promptly if the first is unsuccessful, the number of 'pricks' may be reduced to ten, or even to a single prick.

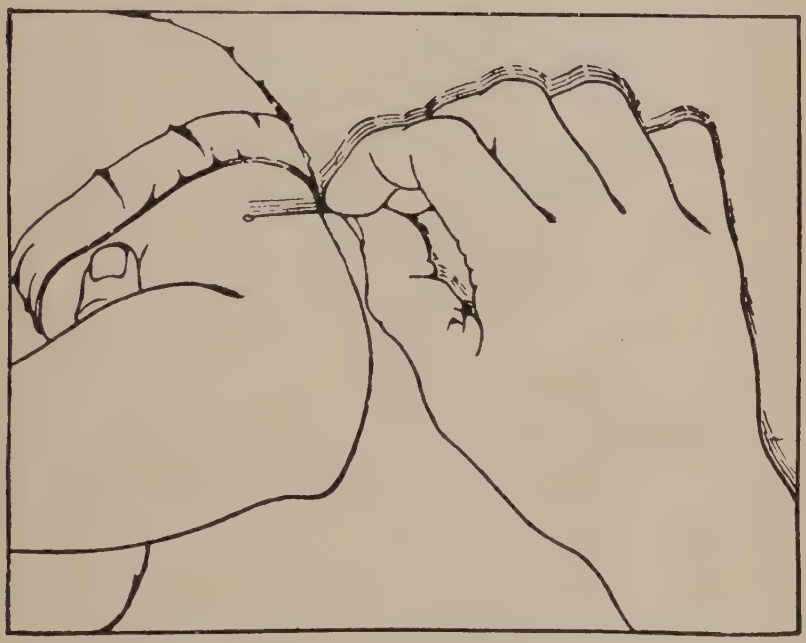


FIG. 5.—The "multiple pressure" method of vaccination. (Leake: Public Health Reports, 1927.)

"The disadvantages of this method, which it shares with some other methods, are: (1) That without demonstration and practice, the technique of applying the proper pressure may not easily be acquired; (2) that without due care an area larger than $\frac{1}{8}$ inch (3 mm.) in diameter may be covered by the insertion. In regard to the first point, the difficulty is usually that the needle is not pressed in the right direction or that the pressure is not firm enough. Provided the needle is held quite tangential to the curve of the arm, and the direction of motion is quite perpendicular to the needle, it is difficult to make the rapid pressures too firmly. In regard to the second point, motion from the wrist with the arm held rigid is usually more accurate than whole-arm motion.

"The advantages of this method are its mildness and painlessness, the fact that it is more rapid than any other effectual and safe method, the fact that no control site is necessary, since the evidence of trauma

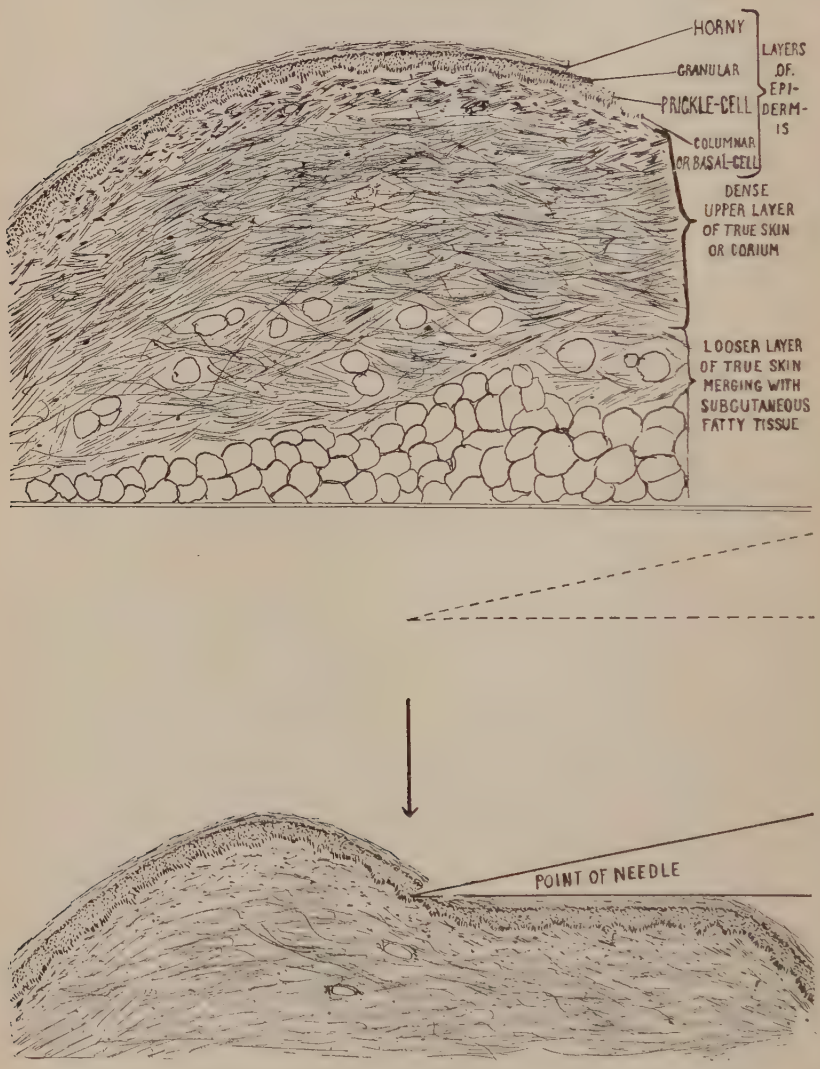


FIG. 6.—Diagrammatic sketch of pressure-prick method of vaccination. The upper part shows the relation of the skin layers before the pressure of the needle has been applied. The lower part shows the motion of the needle from its first position above and parallel to the skin, as indicated by the dotted outline, to its final position pressing against the surface of the skin and entering it slightly. Magnification 25 diameters; to save space the curvature of the surface of the arm is much exaggerated and the perpendicular distance which the needle moves is diminished in proportion to this magnification. (Leake: Public Health Reports, 1927.)

due to the operation has disappeared before the first observation for an early reaction is made and the fact that the vaccine is wiped off immediately, so that the uselessness of a dressing is obvious to the person vaccinated."

Intradermal Method.—Leiner and Kundratitz, Force, Wright and others have advocated the intradermal injection of 0.1 cc. of 1 to 2 to 1 to 100 dilutions of virus (usually 1 to 40) and state that the reaction is milder, fever rare and scars absent or very small, which is especially important in the vaccination of girls. But it is likely to be more painful than the methods described above, and in many instances, even in good hands, the injection will be subcutaneous rather than intracutaneous; subcutaneous applications of smallpox vaccine give reactions which are different from ordinary vaccinia and are not to be differentiated from reactions following other injections, so that one is never sure of the potency of the vaccine being used.

The disadvantage of the method is the absence or very small size of the scars as proof of vaccination and the procedure is to be recommended only in case of danger of autoinfection from eczema or other skin diseases.

Vaccination With Inactivated Virus.—Various investigators have attempted to vaccinate human subjects and the lower animals with virus killed or inactivated by heat and various chemical agents with indifferent success. Gordon[1] has recently reported that an immunity of substantial degree was produced by vaccine virus heated for thirty minutes at 55° C., provided that the virus was of high potency before heating and the dose sufficient. Hunt and Falk[2] also succeeded in vaccinating rabbits with subcutaneous, intracutaneous, intraperitoneal and intravenous injections of virus inactivated by heating at 60° C. for one hour, treated with 0.1 per cent formaldehyde for twelve hours or with immune serum for twelve hours followed by heating, but it would appear that the highest and most lasting immunity follows vaccination with living virus and it is extremely doubtful if vaccination with inactivated virus will ever supplant the usual methods.

Shields.—The vaccine vesicle when formed should be sedulously guarded against mechanical violence or injury. Nature provides an excellent protective covering for the vaccine wound—a hard, concrete, firmly attached crust. This crust is formed by desiccation of the vaccine pock. When the vesicle is ruptured by traumatism some of the contents escape and form an irregular friable crust which is easily detached, leaving an open wound which is liable to infection with pathogenic organisms.

Various forms of shields have been devised to protect the vaccine lesion from injury and infection. Many of these have failed utterly of their purpose, and some have done actual injury by increasing the inflammation, and by rubbing off the scabs and thus producing

[1] Med. Research Council, Special Report Series, 1925, No. 98, p. 135.
[2] Jour. Immunol., 1927, **14**, 347.

open sores; bunion pads are particularly dangerous from the standpoint of tetanus infection. Some writers condemn all shields; we have seen a few made of a light metal like aluminum which appeared to protect the vaccine lesions from the adhesion of the sleeve and from accidental injury without exerting any injurious compression. The use of such a shield, which can be easily sterilized, may be recommended. The application of a sterile gauze compress over the vaccine vesicle is also advocated; there is no objection to this save where the vesicle becomes ruptured, when the crust will adhere to the gauze and be torn off with its removal.

Patients should be advised not to allow the sleeve of the shirt or undershirt to rub against the vaccine vesicle. It is often a good plan to have a thoroughly clean piece of linen sewed into that portion of the sleeve which comes in contact with the vesicle. Caution should be given patients against rubbing, scratching or otherwise fingering the vaccination scab; manipulation of this character is a fertile source of ulceration and late wound infection.

Schamberg and Kolmer[1] have found that daily applications of a 2 per cent solution of picric acid in 50 per cent alcohol upon the vaccinated area after the first forty-eight hours does not interfere with the success of the vaccination and lessens the degree of local inflammatory reaction and constitutional disturbances by hardening the epithelial covering of the vaccine lesion, and thereby decreasing the liability of extraneous bacterial infection.

A point to be emphasized is that severe lesions are unnecessary and are usually due to scratching of the vesicle or pustule and consequent introduction of dirt. No doubt tetanus bacilli may be introduced in this manner, the resulting scab affording the necessary anaërobic conditions for their development.

Number of Insertions.—It is the custom abroad to insert the lymph at several sites. When this is done the scarifications should not be too close, for fear of interfering with the vitality of the intervening skin, thus leading to sloughing. It is best to allow $\frac{3}{4}$ or 1 inch of healthy skin between the lesions. In this country it is the custom to make but a single insertion.

When a person has been exposed to the infection of smallpox it is well to insert lymph from two or three different tubes in different places, so that the fullest opportunity of inducing vaccinia may be offered. It is better that the patient should suffer from a sore arm than from smallpox.

REACTIONS FOLLOWING VACCINATION.

Aside from the trauma due to vaccination three reactions may occur, namely: (1) The *reaction of immunity;* (2) the accelerated or modified reaction (*vaccinoid*); (3) the typical "take" or *vaccinia*. These are

[1] Lancet, November 18, 1911, p. 1397.

detected by observation two days after vaccination and twice later, about four and eight days after vaccination, and by the coöperation of the person vaccinated to observe when the maximum reaction is reached.

Reaction of Immunity.—In a reaction of immunity, which indicates full protection against smallpox, the broadest redness is reached and passed in eight to seventy-two hours after vaccination. The redness is accompanied by a slight elevation of the skin, which can be felt by passing the finger lightly over the vaccinated area. The *time* after vaccination within which the local area of redness and filtration of the skin reaches its maximum and begins to subside, and not the amount of this redness and infiltration, is the index of immunity. The quicker the maximum is reached and passed the higher is the degree of immunity indicated. The *amount* of the reaction depends on the skin reactivity of the person vaccinated, and not on the grade of immunity. It is probable that any reaction which is marked within twenty-four hours will reach its maximum in less than seventy-two hours, and, therefore, would constitute an immune reaction, but some of the most highly immune persons give the smallest reactions.

Vaccinoid.—In the accelerated or modified vaccination or *vaccinoid*, which indicates partial immunity, the broadest redness is reached and passed in three to seven days after vaccination. With a typical primary vaccination, indicating absence of immunity to smallpox prior to this vaccination, the zone of redness, rather narrow from the third to the seventh day, begins a sudden spread about seven days after vaccination and reaches its broadest diameter in eight to fourteen days after vaccination, rapidly disintegrating and disappearing thereafter. These three types merge into each other, all gradations being found in practice; differentiation into the three types is based on the time of broadest redness (Fig. 7). The prompter the maximum the higher is the immunity. Vesicles are formed in vaccinoid and typical vaccinia reactions, but not with the reaction of immunity. The vesicle of a typical vaccinia and of many vaccinoid reactions has a turbid, whitish appearance, but if properly cared for does not become a true pustule, and dries up and heals promptly after the height of the reaction is reached. The characteristic pitted scar is red at first and gradually becomes white. Scars of vaccinoids are much less marked, and reactions of immunity usually leave no scar. All three of the types are successful vaccinations, provided the smallpox vaccine was fresh and strong. All three not only indicate the grade of the previous immunity, but increase the immunity as well. All other results, where proper technique was used, indicate deficient vaccine. Every vaccination should give a reaction.

But a red, slightly raised area, observed at the site of vaccination forty-eight hours after vaccination, does not necessarily indicate that the person vaccinated was immune to smallpox. There are three other possibilities (*Public Health Reports*): "(*a*) The most frequent of

these is that the vaccine used had been weakened by time or temperature, so that, while still able to give the reaction described above, it did not go on to the production of a more marked reaction (vaccinoid), as would a vaccine of full strength if used on the same person. Ordinary ice-box refrigeration is not cold enough for the storage of smallpox vaccine which is to be used in testing immunity.

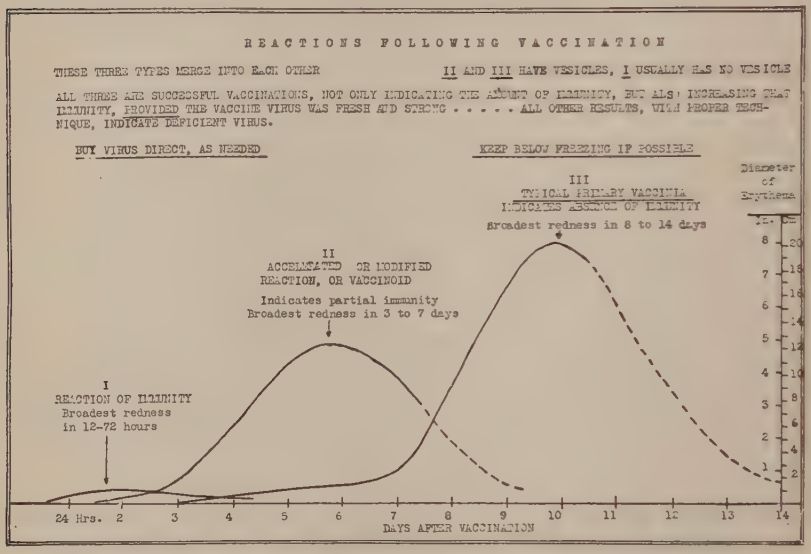

REACTIONS FOLLOWING VACCINATION
THESE THREE TYPES MERGE INTO EACH OTHER
II AND III HAVE VESICLES, I USUALLY HAS NO VESICLE
ALL THREE ARE SUCCESSFUL VACCINATIONS, NOT ONLY INDICATING THE AMOUNT OF IMMUNITY, BUT ALSO INCREASING THAT IMMUNITY, PROVIDED THE VACCINE VIRUS WAS FRESH AND STRONG . . . . . ALL OTHER RESULTS, WITH PROPER TECHNIQUE, INDICATE DEFICIENT VIRUS.
BUY VIRUS DIRECT, AS NEEDED
KEEP BELOW FREEZING IF POSSIBLE
III
TYPICAL PRIMARY VACCINIA
INDICATES ABSENCE OF IMMUNITY
Broadest redness in 8 to 14 days
II
ACCELERATED OR MODIFIED
REACTION, OR VACCINOID
Indicates partial immunity
Broadest redness in 3 to 7 days
I
REACTION OF IMMUNITY
Broadest redness
in 12-72 hours
Diameter of Erythema
24 Hrs. 2 3 4 5 6 7 8 9 10 11 12 13 14
DAYS AFTER VACCINATION

FIG. 7.—Reactions following vaccination. (Leake: Public Health Reports. 1927.)

"(*b*) Accelerated reactions (vaccinoids) usually give at early inspection (second day) the appearance described above, which is similar to that of a reaction of immunity. Thus, even if an early reaction is observed subsequent observations, as on the fifth or seventh day, is necessary to determine whether the reaction was that of immunity, with its maximum diameter of redness reached in less than three days, or an accelerated reaction (vaccinoid) with later maximum. Even a vaccinoid reaction, however, indicates some immunity. Some true vaccinias may show an early reaction, especially if there have been previous unsuccessful attempts at vaccination. Early reactions are more clearly apparent with the multiple pressure method than with other non-injection methods on account of the absence of injury to the true skin and the consequent absence of an obscuring traumatic reaction. Temperature changes, skin irritation and other conditions may cause fluctuations in the diameter of the reaction, and there may even be an almost entire subsidence, giving rise to two maxima. In this case the later maximum indicates the true character of the reaction.

"(*c*) The trauma due to the mere mechanical act of vaccination may cause enough irritation so that the redness persists at the time

of the early forty-eight-hour observation, independently of any specific reaction. To obviate falsely reading such redness as a reaction of immunity, it is necessary either to treat another site as a control, with exactly the same degree of trauma but without applying the vaccine, or, preferably, to use a method such as the 'multiple pressure,' which leaves no traumatic reaction after six hours to obscure faint reactions of immunity.

"An early reaction can be called a true reaction of immunity only when pure smallpox vaccine has been used and these three other possibilities have been eliminated."

THE SYMPTOMS AND COURSE OF VACCINIA.

During the first two or three days after the insertion of the vaccine virus no symptoms are observed beyond those incident to the slight abrasion of the skin made by the operator's lancet. On the third or fourth day very faint redness may be seen around the site of the inoculation. This redness gradually increases while at the same time a distinct papule is formed, which becomes slightly more prominent by increasing in area rather than in height.

FIG. 8.—Infant born of a variolous mother in the Philadelphia Hospital for Contagious Diseases. Vaccinated on day of birth. Protection complete. Photographed on ninth day.

On the fifth day the lesion begins to be vesicular. This is usually observed first upon the margin of the inoculated area. The vesicle gradually increases in size, and the lymph that it contains is at first thin and perfectly transparent. On the eighth day the vesicle reaches its greatest perfection; it is then considerably elevated above the surface of the skin, and presents a "pearly" appearance, although at times the vesicle is yellowish. When examined closely it will be found to

have, even at an early stage of its development, an umbilicated form similar to that seen in the vesicle of variola. The peripheral portion of the vesicle is bulging and prominent, whereas the center is depressed.

About this time there appears around the vesicle an inflammatory band or areola. This is most intense in the immediate neighborhood of the vesicle, gradually merging into the normally tinted skin. During the ninth and tenth days the redness increases; streaks of redness often extend a considerable distance from the lesion. Occasionally the cellular tissue becomes involved in the inflammatory process, producing a swelling and hardness of the skin of the arm. The glands of the axilla, when the vaccination is performed upon the arm, frequently become enlarged and painful.

FIG. 9.—Vaccine vesicles on the eighth day, showing little or no surrounding inflammation. Infant vaccinated at birth, owing to exposure to smallpox.

At the same time mild constitutional symptoms make their appearance. Slight rigors sometimes occur, followed by moderate elevation of temperature. It is not often that the temperature rises more than 1°, 2° or 3° F. above the normal. There are apt to be malaise, impaired appetite and disturbed sleep; but none of these symptoms continue very long. In recording very carefully the constitutional disturbance observed in his first case of induced vaccinia, Jenner says: "On the seventh day he (a boy, aged eight years) complained of uneasiness in the axilla, and on the ninth he became a little chilly, lost his appetite and had a slight headache. During the whole of this day he was perceptibly indisposed, and spent the night with some degree of restlessness, but on the following day he was perfectly well." It cannot be doubted, however, that many children pass through the regular course of vaccinia without any apparent systemic disturbance; our experience leads us to believe that in very young infants, particularly those but a few weeks old, the febrile reaction is less pronounced than in older

children. At times both the constitutional and local symptoms of vaccinia are very severe, especially in secondary vaccinations.

It occasionally happens in severe cases of primary vaccinia that a cutaneous eruption appears at about the tenth day of the disease. This eruption consists of a macular erythema similar to but flatter than the measles eruption. The efflorescence may be comparatively limited in extent or it may cover almost the entire body. On account of its not infrequent association with the vaccine process it has been called *roseola vaccinosa*. An analogous and almost identical eruption, designated *roseola variolosa*, is occasionally seen in modified cases of smallpox just before the appearance of the papules. These eruptions seldom continue longer than two or three days.

FIG. 10.—Vaccine vesicle upon the seventh day; areola just beginning.

On the eleventh or twelfth day of the vaccine process the pock begins to fade. In its declining stage its contents become opaque, desiccation appears in its center and the areola shades off into two or three concentric circles, varying in color from a pale red to a deep red or livid tinge.

By the fifteenth day desiccation is usually completed, although the crust does not fall off, nor can it be easily removed until the end of the third and frequently not until the end of the fourth week.

The completed crust is of a mahogany color, rough on its exterior, thin at its center and periphery, with a thick, circular ridge between. The scar is at first red, but in the course of some months becomes paler than the surrounding skin. It is pitted or foveolated, and not infrequently presents an elevated center from which cicatricial bands radiate to the periphery. A perfectly typical scar looks as if it had been stamped into the skin with a sharply cut die.

As the analogy between cowpox and smallpox is in most respects very close, and as variola frequently differs in the duration and severity of its local manifestations, so also it must be expected that the local lesions of vaccinia will not invariably follow the typical course just described. In some cases the course of the disease is undoubtedly shorter and milder, while in others it is longer and more severe. It is essential, however, that the pock pass through the stages of papule, vesicle and pustule. Likewise, the constitutional symptoms are not uniform; they may not be present at all, or, if present, may be so mild as to pass unobserved.

FIG. 11.—Vaccination performed after exposure to smallpox, showing vaccine lesions about the fourteenth day. Patient was almost completely protected, developing but a few variolous lesions.

Tardy Vaccinia.—Occasionally a retardation of the vaccine process is observed; usually this does not amount to more than a delay of two or three days in the development of the vesicle. In such cases vesiculation is observed upon the seventh or eighth day, and the areola does not develop until the tenth or eleventh day. The development of the pock may be postponed even longer. We have seen patients present no evidence of vaccinal reaction until a week or ten days has elapsed; on such occasions one is apt to conclude that the vaccination is a failure, when, lo and behold, the lesion assumes activity and passes through the normal development of the vaccine pock. We have observed the vesicle to appear as late as one month after the inoculation was performed and then pursue its normal course. Instances have been reported in which the retardation has been much longer.

FIG 12.—First day, showing scarification crust.

FIG. 13.—Fifth day. Vaccination.

FIG. 14.—Vaccine vesicle upon seventh day, showing beginning areola. Patient was suffering from scarlet fever. Vesicle shows some irregularity in form.

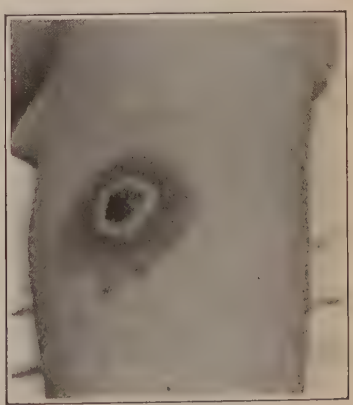


FIG. 15.—Ninth day. Vaccination, showing more pronounced areola.

FIGS. 12 to 15.—Serial illustrations of course of vaccinia.

It not infrequently happens that fresh lymph inserted into an individual who has been some days previously vaccinated with apparent failure will often awaken activity in the old sites of inoculation, and thus the first attempt and the more recent vaccination will both exhibit lesions which run their course at the same time. Bousquet reports a case in which such a revival of a dormant vaccination is said to have occurred three weeks after the insertion of the virus.

A tardy development of the vaccine lesion occurs more commonly with the use of dry virus than with a liquid lymph. A retardation of cowpox in a healthy individual does not in the least impair its protective power provided it runs a regular course. It is evident, however, that a tardy development of the vesicle in one who has been exposed to smallpox might result in most serious consequences, in that the individual might develop variolous symptoms before the vaccine vesicle is sufficiently far advanced to confer protection.

Precocious Vaccinia.—This modification of the normal course of vaccinia is much rarer than retardation of the process. An acceleration of the cowpox vesicle occasionally occurs, the development being hastened by twelve or twenty-four hours. In such cases the usual appearances of the eight-day pock are manifest on the seventh day. These remarks apply, of course, to primary vaccinations; in secondary vaccinations the process is not infrequently hastened and shortened.

A very hasty development of vaccinal reaction in a primary vaccination should direct attention to the possibility of a spurious result, as such lesions not infrequently appear early after the insertion of the lymph.

Accessory or Supernumerary Vesicles.—It occasionally happens that a moderate number of supernumerary pocks are seen in the neighborhood of the vaccine inoculation. Whereas but one abrasion may have been made upon the arm, we now and then observe two or more vaccine lesions develop. At times the accessory pocks never pass beyond the stage of papulation, but at other times they undergo the usual evolution. The fact that such additional pocks observe a predilection for the immediate neighborhood of the original inoculation suggests that they may have resulted from absorption of virus through minute and unobserved abrasions. It is contended by some writers that they are due to transmission of the virus through the lymphatics, inasmuch as they commonly develop at a time when the primary vaccine vesicle begins to fill with lymph. In rare cases vesicles may develop upon other parts of the body, but to this reference will be made later.

Spurious Vaccination.—It is deemed necessary to refer to a spurious variety of vaccine lesion which has grown more frequent of late years, namely, the red *raspberry excrescence*, as it is commonly termed. This growth, when seen, usually appears from three to seven days after the introduction of the virus, beginning as a red elevation at the site of inoculation, quite similar in appearance to the papule of true vaccinia, but instead of advancing to the vesicular stage it remains hard, dense,

bright red in color and nodular in form, looking not unlike a small *nævus*. A thin, friable crust forms on its surface, but when this is removed the lesion continues to present the same general appearance just described. It is very persistent, remaining usually for weeks or even months; no areola forms around it at any time, and it is not followed by a scar.

This peculiar excrescence was described by some of the earlier writers on vaccination; but during the long period in which humanized virus was used exclusively, it was not observed. Since the introduction and general employment of animal vaccine virus it has frequently been seen. It seems, therefore, that it occurs as the result of inoculating the human subject with some unknown form of inert or non-specific material, taken from a vaccinated bovine animal. That this is a spurious form of the vaccine disease, and utterly devoid of protective power against either variola or vaccinia, the writers have had ample opportunities of proving.

The vaccine vesicle sometimes runs an entirely irregular course. In such cases it begins with itching and irritation; instead of being flat and umbilicated, the vesicle is acuminated or conical. The fluid is commonly opaque or yellowish instead of being a clear lymph; as a result the characteristic pearly luster of the vesicle is absent. An irregular areola often develops about the fifth or sixth day; several days earlier, therefore, than in the normal vaccine vesicle. A small scab forms which usually drops off about the tenth day.

Not infrequently the vesicle ruptures early, giving issue to a thin, yellowish fluid which dries in the form of a friable crust. This may become detached and succeeded by a second crust, which results as the first from the desiccation of the exuding material.

INSUSCEPTIBILITY TO VACCINATION.

Occasionally persons are encountered who exhibit an insusceptibility to the virus of vaccinia. The number is, doubtless, much smaller than is commonly believed, for one or two successful attempts at vaccination are often construed to indicate an insusceptibility to the infection.

Gregory says: "The proportion of mankind who exhibit this singular idiosyncrasy is very small. I have seen 30 or 40 such cases in the course of my life. It would be very interesting to determine whether this constitutional inaptitude to cowpox denotes a like inaptitude to receive and develop the variolous poison. In the few cases which I have seen, where inoculation was subsequently tried, the insusceptibility was proved to extend to both poisons, but I have read of instances of an opposite kind."[1]

Of upward of 9000 vaccinations performed at the Blackfriars' station of the National Vaccine Establishment during a period of about ten years following 1859, there was but 1 case which on a second trial was unsuccessful. In this case a third attempt was made, but the child

[1] Lectures on Eruptive Fevers, 1851, p. 244.

was not brought back for inspection, and the result, therefore, could not be ascertained.[1]

There is strong reason to believe that a person may be immune to vaccinia at one period, but later develop a susceptibility to the vaccine disease. Such instances of temporary absence of susceptibility are not particularly rare. Gregory believed that such failures might be attributed to atony of the absorbent system in children exhibiting "slowness of dentition, imperfect ossification of the head, emaciated aspect of the body," etc.; in other words, evidence of rachitis.

It has also been claimed that the existence of certain cutaneous diseases, the eruptive fevers, etc., produces a temporary immunity against vaccinia. This statement scarcely coincides with our own personal experience; owing to the fact that children suffering from scarlet fever and diphtheria are treated in the Philadelphia Hospital for Contagious Diseases upon the same grounds as the smallpox patients, we have been obliged to vaccinate scores and scores of such patients. We have found that the vaccination is recived almost if not quite as uniformly in children with scarlet fever and diphtheria as in those enjoying good health.

In Scotland (1864–1865) 1 of every 200 children proved refractory to three successive vaccinations, thus entitling them to a certificate of insusceptibility. Doubtless many of these children would have responded to vaccination had it been tried some years later.

During the period that vaccination was performed from arm-to-arm successes were so uniform that a person who resisted three attempts on three successive weeks was assumed to be temporarily insusceptible. Such an inference would scarcely be warranted with the employment to bovine lymph, particularly when used in a dry state. Dr. Spalding, Chief Medical Inspector of the Chicago Board of Health, writes that he has known eight, ten, and in one instance in the practice of a colleague—thirteen attempts at vaccination to be made before a successful result was obtained.

Insusceptibility to vaccinia, or rather failure of result after repeated attempts to vaccinate, does not of necessity indicate an insusceptibility to smallpox. We recall to mind a young physician who had been repeatedly vaccinated in childhood and youth without successful result, who on brief exposure to a mild case of variola contracted a severe attack of confluent smallpox. We have also in mind a young woman who fell ill with hemorrhagic smallpox, although she had had seven unavailing trials at vaccination made upon her, three of which were performed within a year preceding the attack of smallpox.

REVACCINATION.

Experience has demonstrated the fact that in a certain number of persons the protection from vaccinia in infancy is permanent, while in

[1] Mentioned by Seaton (Handbook of Vaccination, 1868, p. 196).

others it gradually diminishes and after the lapse of a number of years may become entirely extinguished. The extinction of immunity is evidenced by the large number of persons in adolescent and adult life who are susceptible of revaccination; also by the observation that in all epi-

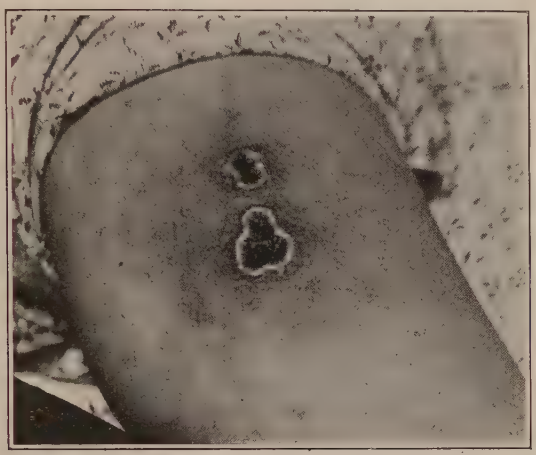


FIG. 16.—Revaccination in an adult, showing vesicles upon the eighth day.

FIG. 17.—Secondary vaccination of doubtful character (twelfth day) followed by a slightly pitted scar.

demics of smallpox a large proportion of the cases occur among persons who were vaccinated in infantile life. The statistics of smallpox hospitals in this country and in England show that from 41 to 78 per cent of the admissions are postvaccinal cases. It is very difficult to determine the proportion of persons vaccinated in infancy that fail of permanent protection, but it is believed to be not far from 75 per cent. Some years ago a very careful observation in a certain American city showed that of 2362 persons revaccinated with reliable virus (no child under twelve years old with a good scar being included in this number) 77.1 per cent were susceptible to some form of vaccinia.

We have no means of ascertaining the age or period of life at which the protection from vaccinia in infancy is liable to diminish or cease entirely, save by applying the test of revaccination or by noting at what age after primary vaccination any considerable number of persons suffer from smallpox. Data tending to demonstrate the latter may be found in the following table:

	Cases.	Deaths.	Percentage of deaths.
Under 1 year:			
Unvaccinated	134	86	64.18
Vaccinated	2	0	0.0
1 to 7 years:			
Unvaccinated	676	280	41.42
Vaccinated in infancy:			
Good scars	11	0	0.00
Fair scars	11	1	9.09
Poor scars	16	1	6.25
Total number vaccinated	38	2	5.26
7 to 14 years:			
Unvaccinated	320	87	27.19
Vaccinated in infancy:			
Good scars	61	2	3.28
Fair scars	24	2	8.33
Poor scars	64	13	14.06
Total number vaccinated	149	13	8.72
14 years and upward:			
Unvaccinated	1742	868	49.83
Vaccinated in infancy:			
Good scars	1864	138	7.40
Fair scars	894	114	12.75
Poor scars	1240	313	25.24
Total number vaccinated	3998	565	14.13

Among over 9000 cases of smallpox admitted to the Philadelphia Hospital for Contagious Diseases during a period of thirty-four years there were only 2 vaccinated patients under one year of age. One of these was a child, aged eleven months, who had been vaccinated two months previously and showed a good scar. The eruption consisted of only six small vesicles, and the child's health was scarcely at all disturbed. The other patient had the disease so indistinctly marked that it was almost impossible to feel certain of the diagnosis of varioloid. An exceedingly modified form of smallpox was occasionally seen

among well-vaccinated children between the ages of one and seven years, but no deaths occurred except where there was a serious complication. The child that died, whose case is classified under the head of "fair scars," was a foundling, aged about one year, badly nourished and very feeble, with a disordered digestion. The eruption consisted of only a very few small vesicles. Death really resulted from inanition. Very little need be said of the cases classified in this age period under the head of "poor scars," as the vaccination in them had been in good part either imperfect or spurious.

The following case demonstrates the difficulty in estimating the genuineness of revaccination. In the spring of 1902 a trained nurse, who had been in attendance upon a private patient suffering from smallpox, was brought into the Municipal Hospital with a mild attack of varioloid. She presented upon her arm a poor mark from a vaccination in childhood. She had been revaccinated a number of weeks before admission with dried virus upon an ivory point. According to her description, a vesicle formed in from two to four days. This itched considerably, and later became surrounded with an areola the size of a silver half-dollar. The axillary glands were distinctly tender. The crust remained upon the sore for a few weeks. The nurse and the physician in attendance regarded the result as a successful vaccination. Upon admission to the hospital the patient exhibited a reddish-brown stain at the site of vaccination, but no true scar. We were convinced that the result had been spurious.

Value of Revaccination.—As to the value of revaccination there can be no question. It is the logical complement of vaccination. Bousquet says very truly that there never has been an epidemic of smallpox since the general employment of Jenner's discovery which has not proved the virtue both of vaccination and revaccination. He adds: "The success of revaccination is at the same time the effect and the proof of the wants of the system; . . . when it succeeds it not only proves that the protective power of vaccination is diminished, but it supplies a remedy for this diminution."

No person should be regarded as having been revaccinated if the secondary vaccination has not been followed by a successful result. Where a revaccination, unproductive of result, is successful when again tried after a brief period of time the probabilities are that the first failure was due to the employment of inert lymph or imperfect technique rather than to insusceptibility on the part of the subject. The failure of a revaccination should not be interpreted as an evidence of certain immunity, but the process should be repeated with carefully selected virus two or three times in order to eliminate all sources of error. When the character of the resulting lesion in a revaccination is doubtful the procedure should be repeated, particularly if the individual is liable to be exposed to the infection of smallpox.

Does insusceptibility to revaccination indicate immunity against smallpox? Jenner, in his "Inquiry," says: "Although the cowpox shields

the constitution from the smallpox, and the smallpox proves a protection against its own future poison, yet it appears that the human body is again and again susceptible of the infectious matter of cowpox." Instances are given of the cowpox twice or thrice taken by persons who could not be variolated either by inoculation or exposure.

Our own experience would lead us to believe that in the great majority of cases insusceptibility to a revaccination carefully performed with good lymph means insusceptibility to smallpox, and *vice versa*. The English Royal Vaccine Commission makes the following conservative statement: "No doubt the want of success (in a revaccination) shows, if the operation has been thoroughly performed, that the person is at the time unsusceptible to the virus, *and it may be to the virus of smallpox also*."

Vaccination After Smallpox.—In one of his later publications Jenner remarks: "Although the susceptibility of the virus of the cowpox is for the most part lost in those who have had the smallpox, yet in some constitutions it is only partially destroyed, and in others it does not appear to be in the least diminished. By far the greater number on whom trials were made resisted it entirely; yet I found some on whose arms the pustules from inoculation (vaccination) was formed completely, but without producing the common efflorescent blush around it, or any constitutional illness, while others have had the disease in the most perfect manner."

We presume that Jenner in this essay refers to vaccination performed a number of years after an attack of smallpox; such results as he observed are quite in consonance with those obtained at the present day. One attack of smallpox will, in the vast majority of instances, protect against a second attack of the disease. Inasmuch, however, as complete immunity is not invariably conferred against smallpox, it is not to be expected that a permanent insusceptibility to cowpox will be produced. Therefore, it is quite possible to successfully vaccinate a certain proportion of persons who have some years before passed through an attack of variola. But, in our experience it is not possible to produce a successful vaccine lesion in an individual who has but recently been the subject of smallpox. We have repeatedly tried to vaccinate persons who have recently recovered from smallpox, but always without success, even in individuals who had never been vaccinated.

RETROVACCINATION OR VACCINATION FROM THE HUMAN SUBJECT BACK TO THE BOVINE SPECIES.

The inoculation of lymph from a human vaccination into the cow produces quite constantly a typical vaccine lesion. This expedient was at one time resorted to with the view of restoring potency to the attenuated lymph of long humanization. Most careful investigators concluded, however, that long humanized virus so transplanted gained

neither in strength nor in purity, and, indeed, became more difficult to retransfer back to the human subject, although this difficulty was overcome in the second human remove. Retrovaccination is seldom employed at the present day.

VACCINAL SCARS.

Physicians are often in doubt as to what constitutes a typical vaccine cicatrix. We deem the subject of sufficient importance to warrant a brief study of the objective features of vaccination scars.

When an individual has undergone a vaccinia which has been perfect in every respect there is left after the fall of the crust a cicatrix which is characteristically distinctive in its features. Such a scar is indicative of the fact that the bearer thereof has passed through the vaccine disease in its most perfect form. The typical cicatrix is round or oval, distinctly excavated, with well-defined margins, reticulated or foveolated, and altogether presenting the appearance of having been stamped into the skin with a sharply cut die. Not all true vaccinations are followed by scars presenting these characteristics, but the more closely the cicatrix approaches to this standard the greater is the assurance that the vaccine disease has been genuine in every respect, and is calculated to give the greatest degree of immunity against smallpox. However, the appearance of the scar may vary within certain limitations and still be regarded as the sequential imprint of a genuine vaccinia.

The variety of vaccine scars is very great; the most frequent variations from the type above depicted are the result of the employment of lymph which has become more or less enfeebled by long human transmission. Modifications of the resulting scar may also be due to abnormalities or complications of the vaccine process and to mechanical injury or interference with the normal development of the vesicle.

In 1851 Decanteleu, of Paris, published an excellent monograph on the subject of vaccine scars, in which the classification is given after the system of Lamarck.[1] The author distinguishes fifteen species of vaccine scars and depicts these and many subvarieties in well-executed drawings, some of which are here reproduced. These drawings represent the type of each species. Fig. 18 represents examples of perfect scars resulting from vaccinations with vigorous bovine lymph or of an early human remove therefrom. The center of the cicatrix is rounded, smooth and convex, and surrounded by a deep, depressed, circular furrow or sulcus, which is traversed by short ridges radiating from the center to the periphery. Most of these scars are round, but occasionally those of oval shape are encountered. Decanteleu found this type of scar in 24 per cent of 5000 scars examined.

It is but natural that vaccine scars should present variations. A

[1] Quoted by Martin, H. A.: Monographie des cicatrices de la vaccine, par J. E. B. Denarp-Decanteleu, Paris, 1851.

cutaneous scar, no matter from what cause, is the result of the destruction of dermal tissue. When merely epidermis is lost no scar results, for the cells of the rete mucosum proliferate and restore the complete integrity of the cuticle. When, however, a portion of the cutis proper is destroyed repair takes place through the formation of fibrous connective tissue, which is scar tissue.

The appearance of a cicatrix will depend upon the character, extent and depth of the tissue loss and sometimes upon certain personal predispositions.

FIG. 18.—Various forms of good vaccinal scars, showing a central, elevated disk surrounded by a furrow with radiating bands; the scars look as if they had been punched out with a die. (After Denarp-Decanteleu.)

FIG. 19.—Smooth scars on a level with the surrounding skin, showing slight pitting; such scars may result from genuine vaccination with long humanized virus. (After Denarp-Decanteleu.)

The minute *foveolations* or *pits* which are commonly seen in vaccine scars, and which are regarded by some as essential to the perfect cicatrix, represent the dilated orifices of hair follicles and sebaceous glands. It is readily seen that if the vaccine process destroys the skin to a sufficient depth the hair follicles and glands may be obliterated and the resultant scar may be devoid of the pits referred to. It is not at all rare to see scars from burns, ecthyma and perhaps also furuncles, which, owing to the presence of numerous pittings, present an appearance which closely simulates vaccine cicatrices.

The peculiar foveations or large, excavated pits seen in the peripheral portion of a vaccine scar probably result from the specific histological changes in the vaccine vesicle, each excavation doubtless representing the floor of a dissepiment or cellular compartment.

The greater the vigor and activity of vaccine lymph, the more inflammatory is the process and the deeper is the tissue destruction. Animal lymph, which is more vigorous than virus of long humanization, produces a larger and deep-seated vaccine lesion and consequently a larger and more pronounced scar. The cicatrix following the use of long humanized virus is often quite small and but little depressed beneath the level of the skin. The depth of involvement of the true skin appears to be inversely proportionate to the number of human removes from the original cowpox source.

Size of Vaccine Scars.—Of 3493 round scars examined by Decanteleu, 1758, or about 75 per cent, had a diameter of 6 to 9 mm. Sixty-three measured 4 mm., 11 measured 20 mm., while the remainder had intermediate dimensions.

With the animal lymph now in use the average diameter of the scar is certainly greater than those studied by Decanteleu. It is not rare to observe scars measuring $\frac{1}{2}$ (12 mm.) to $\frac{3}{5}$ inch (18 mm.), and even 1 inch (24 mm.) and scars below $\frac{1}{3}$ inch (8 mm.) are uncommon.

We occasionally encounter much larger scars which are smooth and glossy and devoid of foveations, which have evidently resulted from sloughing of the skin. While it is quite possible that the vaccine process in such cases has conferred protection, it is impossible, owing to the absence of the characteristic features of the scar, to be sure that such is the case. A large scar, therefore, does not necessarily mean a good scar.

Upon spontaneous detachment of the vaccine crust the underlying scar tissue is seen to be quite reddened. This is, of course, due to the hyperemia or excessive amount of blood in the skin. In the course of some months the color fades away and the scar tissue becomes whiter than the surrounding skin. While the redness persists the scarring is not so easily perceived; later it becomes more visible.

In the course of many years, however, the vaccine scar often loses some of its distinctness and becomes less conspicuous. Indeed, where the original scar has not been pronounced it is possible for it to fade to such an extent that after a lapse of many years it may no longer be visible, but disappearance of the scar is not likely to result where the original vaccinia has been perfect in every respect.

Scars After Revaccination.—The degree of perfection of a revaccination depends, as has been previously stated, on the extent of vaccinal susceptibility remaining in the individual. The more nearly the secondary vaccination resembles a primary vaccinia, the more closely will the cicatrix conform to the standard described above. Revaccinations are, in the vast majority of instances, considerably modified. They produce what has been aptly termed vaccinoid. This modified process is usually followed by a scar which commonly presents upon its

surface minute pittings. Where but little vaccinal susceptibility remains, and the process is greatly modified, it is quite possible that no indelible scar will be left. Usually, however, a pitted scar marks the site of a successful revaccination.

Discolorations are not infrequently seen after unsuccessful attempts at vaccination or revaccination. These are sometimes of a brownish color, representing an increased deposit of pigment; at other times the pigment is lost, leaving a white spot which is neither elevated nor depressed. Occasionally the lines of scarification produced by a pointed instrument will remain visible for a long time, although the vaccination has been unsuccessful.

Prognostic Import of Vaccine Scars.—It has been clearly shown that the degree of vaccinal protection is proportionate to the perfect evolution of the vaccinia. Marson and others of large experience have found that smallpox is less fatal among patients who bear unmistakable evidence, in the form of typical scars, that the vaccine disease has run a perfect course. While Jenner never said very much about the character of the scar, he nevertheless constantly insisted that the vaccinal process should observe a certain definite course in order that the protection should be perfect.

In examining the vaccine cicatrices of a large number of persons, it is found that the scars differ considerably in appearance and degree of perfection; the question arises, Can protection be measured to any degree by the different characteristics of the scars? There is no doubt that many persons with quite inferior vaccine marks are fairly well protected, or even enjoy immunity against smallpox, while some with typical marks prove to be susceptible to the disease, and indeed sometimes perish from it. But such results must be regarded as exceptions to the rule. When a large number of patients are examined and the results tabulated the degree of protection is found to bear a very close and direct relation to the character of the vaccine cicatrices.

All of the patients represented in the subjoined tables were carefully examined on their admission to the hospital, and the number and character of their vaccine scars at once recorded. At this time it was, of course, impossible to foretell the final outcome of the disease. The scars are divided, according to their quality, into three grades, which are designated in the tables by the terms *good*, *fair* and *poor*. Under the first head are included all cases presenting typical vaccine cicatrices, that is to say, cicatrices which are distinctly excavated, with well-defined margins, reticulated or foveolated, and altogether presenting the appearance of having been stamped into the skin by a sharply cut die. Under the second head are included all cases with scars having the same general characteristics, though much less distinctly marked. Under the third head have been classified all cases having scars which were said to have been the result of vaccination, but which in very many instances were so indistinct or uncharacteristic as to make it difficult and sometimes impossible to recognize them as vaccine scars.

In the cases classified under the heads of both *good* and *fair* marks

the patients had all doubtless passed through a well-marked or reasonably well-marked course of vaccinia in infancy. We are strongly of the opinion that very many of the cases classified under the head of "poor cicatrices" were never successfully vaccinated. Very often we felt fully convinced at the time of making the examination and recording the vaccine condition that such was the case, but, as the patients insisted that they had been vaccinated, we could not reject their testimony without being considered, especially by the enemies of vaccination, partial judges. It certainly does not detract from the reputation of vaccination to know that when the vaccine process is irregular, imperfect, or spurious, the protection is diminished or absent. As the mean death-rate of the cases showing *good* and *fair* cicatrices is 8.34, and the death-rate of those showing poor scars is 22.64, it is evident that not only very many of the latter had been imperfectly vaccinated, but that a large number had never been subjected at all to the vaccine influence.

As tending to show that the degree of protection can be measured to a considerable extent by the quality of the vaccine scars borne by persons, the following table of cases of smallpox treated at the Philadelphia Hospital for Contagious Diseases is presented:

	Cases.	Deaths.	Percentages of deaths.
Vaccinated in infancy:			
Good scars	2335	152	6.50
Fair scars	1105	135	12.21
Poor scars	1524	345	22.64
Postvaccinal cases	4964	632	12.53
Unvaccinated cases	3687	1542	41.82
Total	8651	2174	25.13

The opinion has been advanced, more especially by Marson and other English writers, that the degree of vaccinal protection in an individual is directly proportionate to the number of insertions made.

Patients admitted with smallpox.	Number of patients.	Character of scar.	Cases.	Died.	Rate per cent mortality from smallpox after deducting deaths from superadded diseases.	
Having 1 vaccine scar	2001	Good	1032	54	3.83	7.73
		Indifferent	969	134	11.91	
Having 2 vaccine scars	1446	Good	873	32	2.32	4.70
		Indifferent	573	57	8.34	
Having 3 vaccine scars	518	Good	307	7	0.99	1.95
		Indifferent	211	9	3.34	
Having 4 or more vaccine scars	544	Good	358	2	0.55	0.55
		Indifferent	186	3	0.54	
Stated to have been vaccinated, but having no scar	370	...	370	101	23.57	
Stated to have been vaccinated, but particulars of cicatrix not noted	17	...	17	3	6.66	
Total	4896	...	..	402	6.56	

Marson based this opinion upon an extended experience with smallpox, in which he found that the disease was less severe and less fatal in proportion to the number of vaccine scars that the patient presented.

The table on p. 65 published by Marson gives an analysis of all the cases of smallpox admitted into the London Smallpox Hospital between the years 1836 and 1855.

In addition to Marson's statistics the English Vaccination Commission presents observations on 6839 other cases. The figures are as follows:

Scars.	Cases.	Deaths.	Percentages.
1 scar	1357	85	6.2
2 scars	1971	115	5.8
3 scars	1997	75	3.7
4 scars	1514	24	2.2

In summing up, the Commission says: "The evidence appears to point to the conclusion that the greater the number of marks the greater is the protection enjoyed by the vaccinated person in relation to smallpox. This further indication also seems to be afforded, that while the duration in this respect between those with one and those with two marks is not very great, there is a very marked contrast between those with four or even with three marks as compared with those with either one or two."

CASES OF SMALLPOX TREATED IN THE PHILADELPHIA HOSPITAL FOR CONTAGIOUS DISEASES, FROM 1871 TO 1903, INCLUSIVE.

Number of Vaccine Scars and Death-rate.

	Cases.	Deaths.	Percentages of deaths.
Unvaccinated	3220	1392	43.23
Claiming to have been vaccinated; no visible scar	258	150	58.13
Vaccinated seven days or less before variolous eruption	106	39	38.79
Vaccinated longer than seven days before variolous eruption	264	39	14.77
Vaccinated in infancy:			
1 good scar	1282	84	6.55
1 fair scar	695	90	14.39
1 poor scar	1176	293	24.83
Total number showing 1 scar	3153	467	14.81
Vaccinated in infancy:			
2 good scars	486	28	5.76
2 fair scars	182	19	10.44
2 poor scars	153	30	19.61
Total number showing 2 scars	821	77	9.50
Vaccinated in infancy:			
3 good scars	183	11	6.01
3 fair scars	65	4	6.15
3 poor scars	72	14	19.44
Total number showing 3 scars	320	29	9.06
Vaccinated in infancy:			
4 or more good scars	291	25	8.58
4 or more fair scars	95	11	11.57
4 or more poor scars	105	12	11.42
Total number showing 4 or more scars	491	48	9.77

Our own experience on the comparative protection conferred by multiple scars does not entirely coincide with that of the English writers, as will be seen on reference to the table on p. 66.

We believe that the *quality* of vaccine scars is a far more reliable index of the degree of protection than the *quantity*. The table shows that when the scars are typical it makes but little difference whether they are single or multiple, the protection being almost the same. There is no doubt that vaccinia characterized by a single typical vesicle confers immunity against smallpox; it is impossible for multiple vesicles to do more. We have seen some adults with smallpox who bore upon their arms as many as twenty scars from an infantile vaccination; they appeared to be no better protected than individuals with one scar of equal quality.

We have seen a girl, aged twelve years, who had six vaccination scars from infancy, contract smallpox; the six insertions did not seem to confer greater protection than one ordinarily does.

However, as a safeguard against failure when the danger of variolous infection is imminent, it is advisable in vaccinating to make more than one insertion.

The English Vaccine Commission report indicates that patients with foveated scars enjoy an advantage, both as far as the fatality and the mildness of the disease are concerned, over those with unfoveated scars. The data upon which this conclusion is based are, however, too limited to warrant any too great importance being laid upon this point. Furthermore, in the statistics of some outbreaks the figures were by no means conclusively in favor of the foveated class.

There was some evidence to support the view that there was superior protection according as the area of the vaccination marks was larger.

VACCINAL COMPLICATIONS AND INJURIES.

The section on vaccination statistics will indicate the great life-saving power of vaccination. During the past century there have been probably more than 50,000,000 human lives preserved through its beneficent influence. If accidents have now and then attended the practice of vaccination and deaths have resulted therefrom, deplorable though these results may be, they fade into insignificance when compared with the inestimable benefits conferred by this procedure.

In discussing the complications and accidents of vaccination we have tried to preserve a fair judicial attitude. We present the entire list of injuries that have been claimed from time to time to result from vaccination. The list is a long and formidable one and calculated to convey the impression to the mind of the inexperienced that vaccination is a dangerous procedure. We desire to point out the fact that many of the enumerated conditions are excessively rare and that others are not the result of vaccination at all, but are inserted in order to be fairly discussed.

Vaccinal Mortality.—The practice of vaccination is a measure which is not completely and absolutely unattended with risk. It must be

remembered that vaccinia is an infectious disease, and that some danger attaches to the mildest diseases of this character. Furthermore, vaccinia is complicated by the presence of a wound, and cutaneous wounds, particularly if neglected or maltreated, are liable to infection with disease-producing germs. Even a pin scratch has on more than one occasion given opportunity for an infection which has resulted in death.

Most of the injuries and fatalities that from time to time result from vaccination are preventable. Already the use of bovine lymph, special methods of preparation and preservation, an improved vaccination technique, and care of the vaccinated arm have taught us how to avoid most of the vaccinal complications.

Deaths have from time to time resulted from vaccination, but the number is exceedingly small when compared with the enormous number of vaccinations performed.

In England, where antivaccination prejudice is strongest, the alleged death-rate is the highest. According to the Registrar General's return from 1881 to 1889, the number of deaths certified as connected with vaccination was 476, or about 53 a year. Inasmuch as 6,739,902 primary vaccinations were performed during this period of nine years, we have an average death-rate of 1 to 14,159 primary vaccinations. Admitting that vaccination was really accountable for all of these deaths, the mortality-rate is, as Acland has pointed out, still far below that attendant upon the use of chloroform as an anesthetic.[1]

The mortality of vaccination in Germany carefully estimated by Voigt[2] is stated as to have been 35 in 2,275,000 vaccinations (a ratio of 1 death to 65,000 vaccinations), including both primary and secondary insertions. Of the deaths, 19 were due to erysipelas, 8 to gangrene, 2 to cellulitis, 3 to "blood poisoning" and 3 to other causes.

Voigt himself during an experience of twenty years vaccinated over 250,000 people. Within a period of five years he vaccinated 100,000 people with but a single death. This is an evidence of the results that may be expected when all precautions are taken.

Kübler[3] states that in the thirteen years from 1885 to 1897 there were recorded 113 deaths among 32,000,000 vaccinations in the German Empire; 46 of these deaths were shown to have been caused by subsequent wound infection through some neglect on the part of the patient. In only 67 cases was there a connection with the vaccination itself; even in these cases the relation was not proved, but it could not be disproved. Admitting that all of the 113 deaths resulted from vaccination, this would give a rate of 1 death in every 283,177 vaccinations.

When this mortality is compared with the hideous loss of life from smallpox in the prevaccination days, and when it is recognized that properly repeated vaccination is an absolute safeguard against smallpox, the virtues of this procedure can be properly appreciated.

[1] The deaths from chloroform in England are about 1 in every 2000 anesthesias; from ether, 1 in 20,000.

[2] Quoted by Holt: Diseases of Children.

[3] History of Smallpox and Vaccination, 1901.

It is a judicial weakness of human judgment to confound *sequence and consequence*, and the medical mind even in matters medical is not exempt from this failing. It is scarcely to be wondered at, therefore, that laymen with but a hazy comprehension of medical theory and practice should view a succession of events in the light of cause and effect. It would be a difficult matter to prove to the average individual that a cutaneous disease appearing within a few days after the performance of a vaccination was not the result of it.

Vaccination is more universally practised throughout the entire world than any other medical procedure. Probably three-quarters of all civilized people submit to the inoculation of vaccine material in order to be granted immunity against smallpox. In Germany alone, from 1885 to 1897, 32,000,000 people were vaccinated.

In the natural course of events it must occur that among millions of people there will be some in whom the vaccination will have just preceded the development of some disease or other. Laymen and even physicians are too prone under such circumstances to apply the principle of *post hoc ergo propter hoc*. Vaccination immunizes only against smallpox; it will not protect one from tuberculosis, syphilis, skin diseases, etc. Therefore, as these are common diseases, it will of necessity happen that they will from time to time attack persons who have been recently vaccinated. We do not desire to convey the impression that vaccination never does any harm, but we are convinced that many morbid conditions are attributed to vaccination which bear no relation to it save a chronological one.

Vaccination and Cutaneous Disease.—The following classification of skin diseases associated with vaccination is a modification of that formulated by Malcolm Morris and later revised by Frank:

- I. Eruptions attributable to the vaccine virus pure and simple
  - Local
    - Normal vaccinia.
    - Erythematous dermatitis (areola).
  - Constitutional
    - Generalized vaccinia.
    - Diffuse vaccine erythema.
    - Vaccinal roseola.
    - Vaccinal lichen.
    - Vaccinal miliaria.
    - Purpura.
    - Erythema multiforme.
    - Urticaria.
- II. Eruptions attributable to mixed infection at time of vaccination or later
  - Local
    - Erysipelas.
    - Impetigo contagiosa.
    - Furunculosis.
    - Vaccinal ulcer.
    - Localized gangrene.
    - Cellulitis.
  - Constitutional
    - Disseminated gangrene.
    - Syphilis.
    - Leprosy (?).
    - Tuberculosis (?).
- III. Eruption sometimes following vaccination
  - Eczema.
  - Bullous eruptions (acute pemphigus, dermatitis bullosa, dermatitis herpetiformis).
  - Psoriasis.
  - Furunculosis.
  - Urticaria.

The above classification is doubtless faulty in many respects and open to criticism, but will perhaps serve the purpose of indicating in a general way the etiological factors in the production of the various dermatoses that may complicate vaccinia.

Generalized Vaccinia.—This is perhaps the only eruption among those enumerated (with the exception, of course, of the normal vaccine disease) which may with positiveness be attributed to the pure vaccine virus. There are two varieties of generalized vaccinia: (1) Spontaneous generalized vaccinia (vaccinal eruptive fever, vaccinola); (2) generalized vaccinia from auto-inoculation.

Spontaneous generalized vaccinia is an extremely rare condition; many cases formerly regarded as instances of spontaneous diffusion of the eruption are in all likelihood cases of auto-inoculated vaccinia. The eruption appears usually from the fourth to the tenth day after vaccination and most often from the sixth to the ninth day.

The lesions appear in successive crops and pass through the stages of papule, vesicle and pustule. The eruptive lesions, being of different age, may be seen in varying stages of development. Complete subsidence of the efflorescence usually occurs before the twenty-first day. The lesions may be few or numerous and may appear upon any portion of the body surface. Fever is absent in some cases and present in others, being usually proportionate to the extent of the eruption and the associated complications, particularly glandular enlargement.

The causes of generalized vaccinia are but poorly understood. An abnormal susceptibility to the vaccine virus has been invoked as a cause. The administration of the vaccine material through the digestive, circulatory or respiratory system is regarded by Acland as capable of inducing a generalization of the eruption. This writer mentions an observation of Etienne that a generalized vaccinal eruption had been produced in children who had sucked their vaccination pocks; generalized vaccinia has also been produced by the intentional feeding of powdered vaccine crusts to subjects previously regarded as insusceptible to vaccinia.

Chauveau was able to produce a generalized eruption in horses by subcutaneous injection of vaccine lymph and also by administration through the respiratory and digestive tracts.

Generalized vaccinia may present a considerable resemblance to variola. It may usually be distinguished by the absence of an initial stage, its occurrence after vaccination, the appearance of the eruption in crops and the irregular distribution of the lesion. Its differentiation from inoculated variola is rather more difficult.

Generalized Vaccinia from Auto-inoculation.—This form of generalization of the vaccine lesions is by no means rare. Many writers at the present day are inclined to regard the vast majority of cases of generalized vaccinia as due to external inoculation. French writers have reported a number of instances of diffusion of the vaccinal eruption over an extensive cutaneous area, the seat of a moist eczema Unless

there is danger of exposure to smallpox, it is, indeed, advisable to postpone vaccination if the subject is suffering from a dermatosis in which there is denudation of the skin. The number of lesions may be but two or three or there may be a profuse eruption. The development of a few supernumerary lesions in the neighborhood of the original vaccine insertion is by no means uncommon; this may occur even when there is no demonstrable abrasion of the skin. The virus may be transferred by the patient himself through scratching, or it may be conveyed by a second person. Fig. 20 represents six vaccine lesions upon the face of a woman which were produced by the finger-nails of an infant

FIG. 20.—Accidental, multiple vaccinations produced by the scratching of an infant's hand contaminated from a vaccine lesion on its own arm.

in arms; both the mother and child had been vaccinated upon the arm. Accidental vaccine lesions may appear upon any portion of the cutaneous or mucous surface. They may even occur upon the conjunctiva or upon the eyeball. In the latter case there may be loss of vision. One of the writers recently saw in the practice of a medical friend, an ophthalmologist, a case in which a vaccine lesion had been accidentally produced upon the bulbar conjunctiva. The family physician while vaccinating several children was requested by the mother to remove a foreign body from her eye. The physician, without cleansing his hands, everted the eyelids to determine the presence of the offending substance. In the due course of time a vaccine vesicle appeared,

accompanied by tremendous chemosis; the eye was saved only after prolonged skilful treatment.

The lesions in vaccinia generalized by auto-inoculation appear at intervals after the original vesicle is well advanced; they seldom continue to make their appearance after the third week.

Sore Arm.—Under this caption we shall discuss a condition which only in its severer phases is to be regarded as a complication. A certain amount of inflammatory reaction (areola) about the fully developed vesicle is to be viewed as a not undesirable and probably an essential part of the normal evolution of the vaccine lesion. It not infrequently happens that instead of a moderate erythema and edema of the skin, these phenomena are present to an excessive degree. Now and then the inflammation about a vaccination reaches a violent degree of intensity and spreads over a considerable portion or the whole of the affected arm. In such cases the cellular tissue may become implicated, giving rise to a diffuse *cellulitis*. The arm under such conditions is red, swollen, hot, and painful, and there is apt to be some associated systemic disturbance.

In other cases the inflammation is more circumscribed and its force is spent upon the vaccine lesion and the skin in its immediate neighborhood. In such cases a necrosis of the cutaneous and subcutaneous tissues may occur, with the formation of a slough. When this is thrown off an ulcer is left at the site of vaccination. In other cases the vaccinia may pursue a normal course to the development and decline of the areola, but instead of the formation of a typical scab an excavated ulcer appears, covered by a soft, thin crust, which frequently falls off and is renewed, the ulcer persisting in this manner for a long time. Martin, of Boston, repeatedly observed this irregular course upon arms which had been vaccinated with long humanized virus, whereas upon the opposite arm on which bovine virus had been simultaneously employed a perfect result was obtained.

This observation, as well as the scientific investigations of later-day observers, suggests that the excessively "sore arm" is due to the introduction of something in addition to the pure vaccine virus, and, furthermore, that this additional something is of the nature of extraneous microörganisms. The *Lancet* Special Commission on Glycerinated Lymph[1] says that "the presence of a large number of organisms in an active vaccine lymph renders the local lesion more severe," and that "many of the bad results obtained in vaccination are due to imperfect sterilization of the skin and want of protection against the invasion of the weakened and abraded tissues by extraneous organisms." It is also stated that "one of the most certain methods of producing severe edema is for the patient to use his arm freely and to bring about perspiration just before and after the vesicles have begun to form."

It is not uncommon for the arm to become very "sore" as the result

[1] Lancet, 1902.

of thoughtless or accidental traumatism on the part of the vaccinée. The vesicle is frequently ruptured by a blow, friction of clothing, scratching, and other like causes. Where the vesicle is unprotected the shirt sleeve often becomes glued to the vaccination lesion, and attempts at separation cause a detachment of the crust. All of these forms of traumatism doubtless act in the same manner; they prevent the formation of a firm, compact crust which is Nature's protective covering of the vaccine wound. By opening up the wound they permit of infection with extraneous germs which may produce merely excessive inflammation or may lead to ulceration or other more severe vaccinal complications.

Inasmuch as we can obtain a lymph which is rendered free of extraneous germs by the process of glycerinization, by proper care of the arm before, during and after vaccination, we should be able, in the vast majority of instances, to prevent the development of "sore arms."

Vaccinia Hæmorrhagica.—From time to time cases of vaccinia are seen in which the areola about the vesicle at the acme of its development becomes hemorrhagic, assuming the appearance of a diffuse ecchymosis. In some instances the skin beyond the areola may present a bluish appearance. In rare cases there may occur scattered petechiæ and ecchymosis and hemorrhages from some of the mucous membranes. The cause of this complication is obscure; it is doubtless not so much due to any peculiarity of the lymph as to some underlying systemic condition favoring hemorrhagic extravasation, such as scorbutus.

Vaccinal Ulceration. — Ulceration at the site of insertion of the lymph is by no means an uncommon complication of vaccinia. Acland[1] says that nearly 4 per cent of the vaccinal injuries inquired into by the English Local Government Board (1888–1891) were due either to ulceration or glandular abscess. There is in all probability one of two factors which may give rise to vaccinal ulceration—either the introduction into the skin of extraneous microörganisms (at the time of vaccination or later) capable of producing a tissue necrosis, or an abnormal or vitiated state of health which permits of an excessive and unusual local reaction. Both of these factors appeared to play an important role in the production of "bad arms" among the soldiers during the United States Civil War.

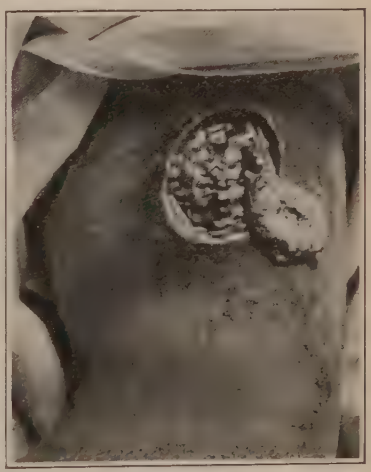


FIG. 21.—Sloughing at the vaccination site accompanying an unusually inflammatory vaccination.

[1] Vaccinia, Allbutt's System of Medicine, p. 596.

We have seen a few cases of ulceration at the vaccination sites following the use of bovine lymph. Fig. 21 shows such an ulceration occurring about the fifteenth day after vaccination.

Septicemia and Pyemia Following Vaccination.—Blood poisoning is a rare condition after vaccination at the present day, and with care in the propagation and preservation of lymph, an aseptic technique and proper protection of the vaccinated arm, this unfortunate complication will doubtless become rarer still. Several appalling epidemics of septicemia after vaccination are on record; one occurred in the United States, one in Germany and one in France. In all three the disastrous results followed the use of *humanized virus;* in two instances there was the grossest negligence in the preservation and preparation of the crusts and in the third a lymph was used which was producing in progressive transmissions increasingly abnormal reactions.

A case of *pyemia*[1] after vaccination is recorded in the *Lancet* (1884, i, 857). A child, aged six months, vaccinated with two other children from the same source, showed on the ninth day appearances of successful vaccination with no unusual symptoms, but on the sixteenth day the sores were ulcerated and freely discharging pus. The child was also suffering from bronchitis. Death took place on the twenty-fifth day after vaccination. The autopsy revealed the presence of pus in the left ankle, right sterno-clavicular joint, both temporo-maxillary articulations and in the bursa over the right olecranon. The lungs presented a number of hemorrhagic infarcts.

Glandular and Subcutaneous Abscess.—In most normal vaccinations enlargement and tenderness of the neighboring lymphatic glands are observed. Where there is an unusual degree of inflammation about the vaccine lesion or actual ulceration the swollen glands not infrequently undergo suppuration. As has been already stated, glandular abscess and vaccinal ulceration comprised nearly 4 per cent of vaccination injuries reported to the English Local Government Board from 1888 to 1891. Sinigar[2] reports 4 cases of abscess among 1160 vaccinations. One appeared on the twentieth day in the lower half of the posterior triangle of the neck, 1 between the pocks on the arm on the twenty-fourth day, 1 on the arm on the twenty-ninth day and 1 in the axilla on the thirty-second day. These abscesses are seldom of serious portent, usually healing rapidly after incision and evacuation.

Localized Vaccinal Gangrene.—In extremely rare instances death of the tissues *en masse* at the site of vaccination may occur, producing a localized gangrene. In cases observed by Balzer, Wheaton and Acland the children were of syphilitic parentage. Hutchinson, however, saw 3 cases of vaccinal gangrene in children in whom no such cause could be invoked. The view that the condition of the tissues is the most important etiological factor in the production of this complication is corroborated by the experience of surgeons in the Confed-

[1] Mentioned by Poole (Vaccination Eruptions, Edinburgh, 1893, p. 118).
[2] Lancet, 1902.

erate army during the United States Civil War. Dr. Joseph Jones[1] writes: "After careful inquiry we were led to the conclusion that these accidents were, in the case of Federal prisoners, referable wholly to the scorbutic condition of their blood and the crowded condition of the stockade and hospital. The smallest accidental injuries and abrasions of the surface, as from splinters or bites of insects, were in a number of instances followed by such extensive gangrene as to necessitate amputation. The gangrene following vaccination appeared to be due essentially to the same cause, and in the condition of blood of these patients would most probably have attacked any puncture made by a lancet, without any vaccine matter or any other extraneous material."

Vaccinia Gangrænosa.—As has been pointed out by Crocker and others, the term vaccinia gangrænosa is a misnomer, inasmuch as the affection recorded under this title occurs after varicella (varicella gangrænosa) and other discrete pustular eruptions. Disseminated necrosis of the skin which in rare instances follows vaccinia, varicella and pustular dermatoses may occur independently of these diseases in apparently healthy infants; a better designation, therefore, for this condition is *dermatitis gangrænosa infantum*. The gangrenous changes in the skin may occur early or late. Stokes,[2] of Dublin, reports a case of so-called vaccinia gangrænosa developing forty-eight hours after vaccination. The vaccinal or varicellous pustules may be directly converted into blackish sloughs, which are thrown off and leave deep, excavated ulcers; or the gangrene may not set in until a week or two has elapsed, beginning as papulo-pustules which crust over, become surrounded by an areola and then break down and ulcerate. High fever is often present. The cause of this rare condition is obscure; it usually supervenes in the course of some pustular febrile disease,[3] particularly in tuberculous, syphilitic or rachitic children. It is quite possible that the gangrene is due to infection with some virulent microörganism.

Vaccinal Roseola (*roseola vaccinosa, vaccinal rash,* or *erythema*).—Under the above designations has been described a rosy, macular rash, which occasionally appears in vaccinated persons about the time of maturation of the vesicle. While this eruption is ordinarily seen about the tenth day after vaccination, it has been observed as early as the third day and as late as the eighteenth. It usually appears first upon the vaccinated arm, rapidly spreading to the trunk and other portions of the body. The macules are large, irregular, blotchy in appearance, of a rosy tint and not elevated above the level of the skin. In rare instances the macules may coalesce, giving rise to a *diffuse erythema*.

[1] Report of Louisiana Board of Health, 1883–1884.

[2] Quoted by Crocker: Dublin Jour. Med. Sci., June, 1880.

[3] The writers recall the case of a young girl suffering from smallpox, who developed at the end of the third week numerous punched-out areas of cutaneous gangrene. The patient succumbed to this complication, which was doubtless a condition analogous to the so-called vaccinia gangrænosa.

FIG. 22.—Roseola vaccinosa appearing upon the tenth day after vaccination.

FIG. 23.—Vaccination upon the tenth day, showing an unusually intense areola. A papular vaccinal eruption is also seen upon the face.

The eruption is of brief duration, lasting from a few hours to a day or two. It may be accompanied by moderate elevation of temperature.

The rash is not unlike that of measles, with which, indeed, it has not infrequently been confounded. The eruption of measles is more elevated, being maculo-papular in character and more persistent, and is accompanied by higher fever and the characteristic catarrhal symptoms of this disease.

During epidemics of smallpox vaccinal roseola has been mistaken for the beginning eruption of confluent smallpox. *Roseola vaccinosa* has a complete analogue in the *roseola variolosa*, an exanthem presenting almost identical features, which is not infrequently observed just before the appearance of the eruption of modified smallpox.

Vaccinal Lichen.—Crocker states that in his experience vaccine lichen has been the most common of the true vaccinal exanthema. He has made notes of 20 cases of this eruption. He states that it may be either papular, papulo-vesicular or pustular. It appears from the fourth to the eighteenth day, most commonly on the eighth; in about one-half the cases it is seen first on the arms, appearing in the remainder on the trunk, neck or face; the eruption then extends in successive crops over large portions or the entire cutaneous surface (Fig. 23).

The papules are reddish, conical, pin-head sized, surrounded by a reddish halo and often surrounded by minute vesicles or pustules. In the experience of the writers vaccine lichen has been excessively rare.

Vaccinal Miliaria.—In rare cases instead of a papular eruption a vesicular outbreak may take place, usually from the eighth to the eleventh day. Danchez[1] writes: "We give the name vaccinal miliaria to a satellite eruption of the vaccinal fever, appearing from the eighth to the twelfth day (very rarely later) after vaccination. It is constituted by small vesicles of the size of a grain of millet, accumulated in great numbers over large surfaces, containing a transparent liquid at first, then opaque, followed by slight furfuration, and never leaving cicatrices after it."

A miliary vesicular eruption is occasionally seen in or around the vaccination areola. These vesicles are not true vaccine lesions, for Martin has shown that the contents inoculated upon another individual fails to produce the vaccine disease.

Erythema Multiforme and Urticaria after Vaccination.—The eruption of multiform erythema is occasionally seen in vaccinated individuals between the first and the tenth day after the insertion of the virus. In some cases the eruption is delayed considerably beyond this period. The lesions may be erythematous, papular, tubercular, vesiculo-bullous or mixed.

At times the eruption is annular. Crocker saw a well-marked case which began on the ninth day after vaccination, and was characterized by shilling-sized annulo-papular patches. Napier observed a case on the eleventh day which began as rings.

[1] Vaccinides, Thèse de Paris, 1883.

Not infrequently urticarial lesions are present, the eruption being a type of combined erythema multiforme and *urticaria*. Allen and Sobel regard urticaria as one of the most common of the generalized vaccinal eruptions.

Norman Walker[1] has observed 5 cases of erythema multiforme after vaccinations with glycerinated lymph. In all, the early course of the vaccination was uneventful. The eruption was invariably seen on the hands and face, but on other parts as well.

In a review of the vaccinal complications in 1160 vaccinations, Sinigar[2] states that there were 23 cases of erythema, including simple erythematous blushes, finely punctate erythemata, erythema of papular or urticarial type and erythema multiforme. Concerning the date of appearance, 1 rash appeared on the third day, 5 on the eighth day, 2 on the ninth, 5 on the tenth, 4 on the eleventh, 1 on the twelfth, 4 on the thirteenth and 1 on the sixteenth day. No age was exempted; in 4 cases the patient was over seventy years of age. The average during of the rash was forty-eight hours, but in one severe case it lasted six days.

FIG. 24.—Secondary impetigo engrafted upon a late vaccination and subsequently upon other regions.

Impetigo Contagiosa.—This contagious disease of the skin is extremely common, independent of vaccination, among dirty and poorly

[1] British Med. Jour., 1901, p. 1201. [2] Lancet, 1902.

nourished children. Any abrasion of the skin increases the liability to its development. Its occasional occurrence after vaccination, particularly among children in poor hygienic circumstances, is, therefore, scarcely to be marvelled at. The introduction of the infection of impetigo with the insertion of the vaccine virus must be an occurrence of the greatest rarity; inasmuch as impetigo sores develop rapidly (from one to two days) after the skin is infected, we would expect, if the disease were invaccinated, to discover the impetigo lesions twenty-four to forty-eight hours after the vaccination.

As a matter of experience, however, impetigo usually develops at a considerably later period; it may make its appearance at any period up to the complete healing of the vaccinal wound. It is not infrequently observed at the end of the second or third week after vaccination. The first lesions are usually seen about the site of insertion of the vaccine lymph. This area may become quite inflamed, the surrounding epidermis raised up by a sero-purulent fluid and the process extend upon the periphery, with the production of voluminous ochre colored crusts. From this as a focus other portions of the skin become infected by auto-inoculation through scratching or other means. At times impetigo may assume a bullous form, simulating pemphigus; most of the pemphigoid eruptions after vaccination would appear, however, to belong to the group of bullous dermatitis presently to be described.[1]

In 1885 an outbreak of a cutaneous disease, said to have presented the clinical features of impetigo, occurred in villages on the Island of Rugen, in the Baltic Sea, after the vaccination of 79 children.

Impetigo contagiosa is caused by invasion of the skin with the germs of contagious pus, independently of its source. There are probably two chief varieties due respectively to the Streptococcus and Staphylococcus pyogenes.

Vaccinal Erysipelas.—Erysipelas is an acute infectious disease resulting from invasion of the body with a specific streptococcus. In the vast majority of cases of this malady the infection gains its entrance to the system through a wound of the cutaneous or mucous surfaces; the disease therefore is essentially a wound infection.

Inasmuch as vaccinia is attended with the production of a wound of the skin, it is not surprising, particularly in view of the frequent neglect of vaccination wounds, that erysipelas should occasionally occur after this procedure. The erysipelatous infection is usually conveyed to the vaccination wound at some period subsequent to the insertion of the vaccine virus; in rare cases, however, the specific germs of erysipelas

[1] Engman and Grindon have each described (Jour. Cutan. and Genito-urin. Dis., 1901, pp. 180 and 188) extensive cases of bullous impetigo, not, however, related to vaccination. They state that this form of the disease is quite common in St. Louis and that epidemics occasionally occur in foundling asylums, attacking particularly weak and undernourished infants. Some of the cases reported terminated fatally. (The differential diagnosis between bullous impetigo, acute pemphigus and dermatitis herpetiformis is sometimes fraught with difficulty.)

may be present in the lymph, in which event this complication develops on the second or third day after vaccination.

Erysipelas may develop in an infant after vaccination and still be independent thereof. Erysipelas is a common disease among infants; according to Dr. Ogle's testimony before the British Royal Vaccination Commission, 2000 per 1,000,000 infants under three months of age perish from it. It has been known to develop after very trivial injuries, such as the scratch of a pin, abrasion from the friction of clothing, etc.

Both vaccinal erysipelas and erysipelas from other causes are attended with a rather high mortality-rate in infants. Of the deaths attributed to vaccination in England between 1886 and 1891 almost one-half resulted from erysipelas.

Erysipelas may result from the employment of lymph containing streptococci, from infected instruments, unclean hands, contact of soiled linen, or from previous contamination of the skin at the vaccination site.

As a vaccinal complication, erysipelas appears to be distinctly on the decrease. In 1877 Lotz was able to collect in Germany but 2 cases of death from this cause in 1,252,554 vaccinations.

The increased attention to asepsis in vaccination, the careful protection of the vesicle when formed and the employment of bovine lymph will doubtless continue to lessen the frequency of this complication.

It is claimed that animal virus, on account of the comparative insusceptibility of the bovine species to erysipelas, gives a greater security against this disease than humanized virus.

True vaccinal erysipelas should be trenchantly distinguished from the dermato-cellulitis which is not infrequently observed about the vaccine lesion, and which occasionally involves the entire upper arm and even the forearm; this is nothing more than an exaggeration of the inflammatory areola.[1] The arm is swollen and intensely reddened, but there is no tendency for the process to spread to other parts of the body, the inflammatory phenomena subsiding after the height of the vaccinia has been reached.

Tetanus Following Vaccination.—The development of lockjaw after vaccination was until a few decades ago an occurrence of the greatest rarity. The minority contingent of the British Royal Vaccination Commission in 1896, after extended investigation, was able to mention but a single instance of this complication.

Tetanus after vaccination is said to be unknown in France, Germany and other continental countries of Europe.

Even though the number of cases of tetanus among the vaccinated constitutes but a minute fractional percentage, the disease is so fatal that no effort should be spared to ascertain the manner in which the germs have gained entrance to the wound, in order that this unfortunate complication shall in the future be prevented.

[1] Some of the older writers, including Jenner, referred to this condition under the rather misleading designation of "erysipelatous inflammation;" but, as Jenner himself explains, it was not regarded as true erysipelas, but as merely bearing a resemblance to it.

The Pennsylvania State Vaccination Commission, of which one of the authors was a member, had testimony presented to it on the habitat of tetanus germs in Nature, on the geographical distribution of tetanus in the United States, on the character of wounds in which tetanus may develop and on kindred topics. A consideration of these is essential to a proper study of the causes of vaccinal tetanus.

The tetanus bacillus is a common germ, found in most garden earth, in dust, in manure and in the intestinal discharges of certain animals.

Tetanus has occurred after a great variety of injuries in which a wound has been inflicted upon the skin, even when the wound has been of the most trivial character. It has occurred after mosquito bites, bee stings, extraction of tooth, compound fractures, splinter in the finger, splinter of bone in the throat, all sorts of surgical operations, burns, confinements, hypodermic injection of drugs, etc. Infection of the navel in new-born infants is one of the most frequent causes of tetanus.

In the nine years from 1903 to 1911 Pennsylvania had 152 cases of Fourth of July tetanus—more than any other state in the Union. In fact, Pennsylvania has always been a high tetanus state. Of 1099 cases of tetanus from all causes occurring in forty-one states, over a period of years, the highest number (224) developed in Pennsylvania. Pennsylvania, New York, New Jersey and Maryland had, together, more than 50 per cent of the cases of tetanus in the entire United States. It would seem, therefore, in these states the liability to contract tetanus from various causes is greater than in other sections of the country.

The study of the period of incubation of ordinary tetanus and of the mortality-rate of the acute and chronic cases is of interest in connection with the subject of vaccinal tetanus. Of 870 cases studied by Anders and Morgan, 568 developed tetanus between the first and tenth days after infection. The largest number developed the disease on the seventh day. Three hundred and two cases developed tetanus in from ten to twenty days and over.

It is pretty well established that the cases with short incubation periods have a very high mortality, whereas the long incubation periods are much less fatal. Of the 568 cases, with an incubation period of ten days or under, 419 died, representing a fatality of 73.8 per cent. Of the 302 cases with an incubation period of ten to twenty days and over, 45 died, a fatality of 11.5 per cent. The difference is most striking and tends to show that the longer the time elapsing between the entrance of the tetanus germ and the development of tetanus symptoms, the less fatal is the disease.

Willson, in a study of 52 cases of vaccinal tetanus, collected from literature and other sources, has shown that the vast majority of cases of vaccinal tetanus have an incubation period of over two weeks and a majority over three weeks. The average period of incubation of vaccinal tetanus is about three weeks, which is about two weeks longer

than the average period of incubation of tetanus from other causes. This discrepancy is worthy of comment.

Of greater significance, however, is the fatality of vaccinal tetanus. In Willson's cases it was 78 per cent. Now this is not the mortality-rate of tetanus of long incubation period, which was under 12 per cent, but does approximate very closely the mortality of the short incubation period cases, which was 73.8 per cent. This leads us to inquire, Were the cases of vaccinal tetanus in reality not short incubation period cases, *i. e.*, was not the infection of tetanus introduced subsequently, when the vaccination was in the most favorable condition to receive a secondary infection?

Willson made a detailed inquiry into the circumstances surrounding the cases of vaccinal tetanus reported by him, and concluded that in every case in which the particulars were known, over-abundant opportunity was offered for secondary infection.

It should be here stated that Prof. Joseph McFarland, in a paper entitled "Tetanus and Vaccination: An Analytical Study of Ninety-five Cases of this Rare Complication," written in 1902, came to a conclusion contrary to that reached by Dr. Willson; he believed that in the group of cases occurring about 1901 the tetanus organisms were, in his opinion, in the virus. The argument made, required the support of two hypotheses to explain away the discrepancies in the incubation period and the mortality-rate. The truth of these hypotheses remains unproven.

Great light has been shed upon this subject by carefully carried out experiments in the Hygienic Laboratory of the United States Public Health and Marine Hospital Service. Dr. John F. Anderson, Director of the Laboratory, testified before the Commission that experiments had been carried out on monkeys and guinea-pigs (both of which are susceptible to tetanus), in which vaccine lymph purposely contaminated in the laboratory, with countless numbers of tetanus spores, was used. The vaccinations of the monkeys and guinea-pigs were more severe than the ordinary vaccinations performed on man, in that several places were inoculated and the areas abraded were large. It was found impossible to communicate tetanus in this manner. Dr. Anderson, when asked what conclusions he drew from these experiments, replied: "My conclusion from these experiments is that it is almost impossible (I would not say it is impossible, although I almost feel that way) to produce tetanus, even with vaccine virus that contains tetanus germs in it, by the simple act of vaccination." (Twenty-ninth Session; answer to question 28.)

Prof. William H. Welch, of Johns Hopkins University, said *apropos* of this subject: "I would like to call your attention to the fact that even if the tetanus bacillus or its spores should by an accident get into the lymph, the chances would be probably 99 out of 100 that it would never be heard from."

In 1901 Dr. Robert N. Willson, of Philadelphia, on examining about

100 specimens of vaccine lymph, cultivated from one glycerinated point "bacilli and spores resembling those of tetanus." He cultured these in artificial media and injected them into animals producing symptoms strongly suggestive of tetanus. It must be recognized, however, that the said germs in this vaccine virus were cultivated in a tube of bouillon, where they could develop their toxin and the cultured bouillon was then injected into animals.

Dr. Anderson's researches make it almost positive that vaccination of susceptible animals with the virus itself would have been innocuous.

It is doubtful whether tetanus follows vaccination oftener than it does other wounds of a similar character. Dr. Cressy L. Wilbur, Chief Statistician of the Census Bureau, Department of Commerce and Labor, states that in 1910, 1373 people died from tetanus from all causes in the registration area of the United States, covering a population of 53,000,000 people. During the same period and in the same area there were 16 deaths from vaccinal tetanus, or a little over 1 per cent of the total number.

Dr. William S. Wadsworth, one of the coroner's physicians of Philadelphia, testified that from 1905 to 1912, 174 cases of fatal tetanus were reported to the coroner's office of Philadelphia. Of these, 13 were cases of vaccinal tetanus. Several of these patients were not residents of Philadelphia, but were brought to hospitals here for treatment and died in this city. While this percentage of vaccinal tetanus to tetanus from all causes is much larger than represented by the Federal figures, this may be due to the elimination from the coroner's records of tetanus of the new-born, which is the most frequent form of tetanus. Vaccinal tetanus is thus seen to be a rare complication; 13 persons, not all from this city, died in Philadelphia during a period of eight years. While such deaths are greatly to be deplored, they must not blind us to the infinitely greater evil which vaccination banishes. From 1901 to 1904, inclusive, 890 persons perished from smallpox in Philadelphia.

Since 1909 there were examined in the Hygienic Laboratory of the United States Public Health and Marine Hospital Service, approximately 100,000 specimens of vaccine virus, particularly with the purpose of determining the presence of tetanus germs or their products. The vaccine was purchased in the open market and the examinations were made as thoroughly as it is possible to make them. To employ Dr. Anderson's words: "We have never succeeded in finding any evidence of the presence of the tetanus organism or its products in vaccine virus."

All vaccine propagators, licensed by the United States Government, have been obliged since the Act of 1902, to make careful tests to exclude the presence of tetanus organisms in vaccine virus. These tests not only consist of making cultures of the virus, but also the injection of the virus into susceptible animals. These safety tests are, to be sure, concluded before the virus is placed upon the market.

Dr. Armstrong,[1] after an experimental study of the subject of shields, comes to the following conclusions:

1. Epidemiological evidence indicates that postvaccination tetanus, when it develops, tends to follow severe primary vaccinations performed with large insertions and dressed with some type of shield or covering strapped to the site.

2. Shields and dressings are shown markedly to predispose to the development of postvaccination tetanus in monkeys and rabbits vaccinated with virus artificially contaminated with Bacillus tetani.

3. A proper vaccination is defined as one in which the insertion is not over $\frac{1}{8}$ inch in its greatest diameter, made by some method which does not remove or destroy the epidermis. *Such insertions treated openly, i. e., without the use of shields or dressings strapped to the site, have never, in so far as we are aware, been followed by postvaccination tetanus.* It seems probable that the adoption of these simple procedures of technique on the part of vaccinators, coupled with a proper warning to the vaccinated individual, or his parents or guardian, concerning the dangers of home-applied shields and dressings, would eliminate tetanus as a complication of vaccination.

Tetanus Germs in Bunion Pads.—Armstrong[2] reports on tetanus following the use of bunion pads as vaccination dressing. He states that 11 cases of tetanus developed after the use of bunion pads employed as vaccination shields. About 200 such pads were bought in the open market and collected from different sources. In 25 per cent of the pads bacteriological studies determined the presence of tetanus germs.

It is interesting to note that in the only case of vaccinal tetanus reported in England for many years a bunion plaster was used as a dressing. (Findley and Findley, 1902.) This complication is so rare in England that, according to Acland, there was only 1 case after 5,000,000 consecutive vaccinations.

Considering the hundreds of thousands of vaccinations which are performed each year, and the neglect of the vaccination wound on the part of many persons, the wonder is that not more cases of tetanus develop. Where the vaccinia runs a perfectly normal course, and the vesicle is uninjured and the crust undisturbed, tetanus is much less prone to develop. Tetanus would appear to occur no oftener, if as often, after vaccination than after ordinary cutaneous wounds.

In at least three instances in which tetanus followed vaccination the same virus was used upon other persons in addition to the one that developed the disease. In a case investigated by the British Royal Vaccination Commission "a female child, aged two months, developed trismus on the twenty-third day after vaccination. This child was vaccinated from the arm of a female infant, aged five months, and *at the same time and with the same lymph 6 other children were vaccinated, and none of them developed tetanus* or sore arms."

[1] Pub. Health Repts., 1927, No. 50, vol. **42**.
[2] United States Pub. Health Ser. Repts., June, 1926, p. 195.

In a case of tetanus occurring in a woman, aged twenty-one years, reported by Drs. William Findlay and J. W. Findley,[1] several people were inoculated with virus from the same tube, but none save the one patient developed tetanus. In one of the Camden cases the patient's "brother was vaccinated from the same tube, the vaccination proving successful and normal." These cases would certainly seem to indicate that the tetanus organisms were not derived from the vaccine virus employed.

Nerve Complications.—Winnicott and Gibbs[2] report a case in a child, aged five months, who on the sixth day after vaccination against smallpox became drowsy and showed a squint. Later, drowsiness alternated with restlessness, facial paralysis, left ptosis and internal strabismus, fever. Still later clonic convulsions developed; the patient became stiff and resistant, with complete loss of consciousness. Symptoms abated gradually and the patient made an absolute recovery without sequelæ. Forty-four other cases of encephalitis following smallpox vaccination are reviewed. Of the entire series of 45, 21 were fatal. These 45 cases fall into four groups: (1) Cases reported resembling a type common in epidemic encephalitis lethargica; (2) the Dutch group (35 cases), with vomiting, somnolence, convulsions, high mortality, but no paralysis, except in 1 case; (3) Lucksch's group (also 1 case reported by Blano and Caminopetro) with trismus as a frequent sign; (4) Stiner's case in Switzerland resembling serous meningitis. Postmortem examination of several fatal cases showed encephalitis. The absence of sequelæ distinguishes these cases from epidemic encephalitis.

Leiner[3] refers to recently reported cases of encephalitis and meningitis following vaccination for smallpox, and reports 3 cases under his observation. The patients in these cases were from seven to ten years of age. In 2 of the cases the symptoms were those of meningitis, and the cerebrospinal fluid findings indicated a meningitis of the serous type, except that in this case there was a considerable increase in the cells. In the third case the symptoms indicated involvement of the brain, spinal cord and peripheral nerves, and the diagnosis of meningoencephalitis disseminata with neuritis nervi ulnaris was made. All the patients recovered. The symptoms in all these cases developed at the end of the second week after vaccination, but the children had not been in normal condition following vaccination. From his study of these cases and other cases reported the author concludes that: There is an increase in the number of cases of this type following vaccination as the virulence of the lymph used increases. Vaccination encephalitis and meningitis appear more frequently in older children vaccinated for the first time than in infants. Vaccination encephalitis

[1] Lancet, February 22, 1902.
[2] Vaccine Encephalitis, Brit. Jour. Child. Dis., 1926, **23**, 119.
[3] Cerebral Symptoms Following Smallpox Vaccination, Med. Klin., 1926, **22**, 441.

is similar to encephalitis following other infections and may be comparable to generalized vaccinia.

The last statement is open to doubt. Winnicott and Gibbs, quoted in the article on chickenpox, refer to 8 cases of encephalitis, 2 of meningismus and 2 of myelitis following varicella. Inasmuch as chickenpox, smallpox and other infectious diseases are at times followed by encephalitis and myelitis, it is a question whether these as well as vaccination may not act by lowering the general resisting power. During epidemics of encephalitis in a community it would be wise to postpone vaccination unless smallpox be also prevalent.

Vaccinal Syphilis.—The study of vaccinal syphilis has been bereft of much of its importance since the general adoption of calf lymph for vaccination. Inasmuch as the bovine species is totally insusceptible to the syphilitic infection, it is obviously impossible to convey this poison by vaccination with lymph from this source.

With the employment of *humanized virus* and particularly with arm-to-arm vaccinations, it must be frankly admitted that, though relatively of extremely rare occurrence, it is possible to convey the syphilitic poison. The infrequency of this lamentable accident may be comprehended when it is stated that Dr. Robert Lee saw but 1 case of supposed vaccinal syphilis among 30,000 children at the Hospital for Sick Children, Great Ormond Street, London, an institution particularly likely to attract cases of syphilis. At the East London Hospital for Children, Dr. Radcliffe Crocker, although for many years on the lookout for such cases, never observed a single instance of vaccinal syphilis.

In 1856, the London Board of Health collated the experiences and opinions of a large number of prominent physicians concerning vaccinal syphilis. None of the respondents were able to present any convincing facts, and a large majority expressed complete incredulity as to its occurrence. The English Royal Vaccination Commission, referring to this incident, remarks: "It is impossible to believe that an event concerning the possibility of which almost all the leaders of the profession were in 1856 incredulous can be otherwise than extremely rare."

The commission in its judicial sessions examined many physicians who had extensively practised vaccination for many years, and who had never personally observed vaccination syphilis themselves or heard of it in the immediate practices of their colleagues.

Epidemics of vaccinal syphilis have been observed and reported by Marcolini (1814 in Udine), Cerioli (1812 in Cremona), Tassani (1841 in Grumello), Wegeler (1849 in Coblentz); Oberfranken (1852 in Freienfels), Marone (1856 in Lupara), Pacchiotti (1861 in Rivalta), Depaul (1866 in Morbihan, France), Kocevar (1870 in Schleinitz and St. Veix), Jonathan Hutchinson (1871 in London, two series of cases) and Layet (1880 in Algiers and 1885 in Turin).

More than one-half of the cases of vaccinal syphilis that have been recorded have occurred in Italy. The remainder have been found in

France, Germany and England. Fortunately, such infections in the United States have been extremely rare. It has been estimated that the aggregate number of cases of vaccinal syphilis that have occurred is about 700. When we think of the millions of lives that have been saved by vaccination during the past century, we recognize the fact that the sacrifices, however deplorable, have been relatively small. Many blessings are leavened with misfortune.

The British Royal Commission on Vaccination says: "Absolute freedom from risks of syphilis can be had only when calf lymph is used, though where the antecedents of the vaccinifer are fully ascertained, and due care is used, the risk may for practical purposes be regarded as absent."

The employment of calf lymph and the complete elimination of the risk of transferring syphilis to the vaccinée have robbed the opponents of vaccination of one of their most potent arguments against the enforcement of vaccination.

In 1927,[1] the heads of the United States Army, Navy and Public Health Service, General Ireland, General Stitt and General Cumming, issued a pronouncement to the effect that false statements had been circulated that might cause some people to fear that vaccination against smallpox might cause syphilis. They stated that with the use of calf vaccine "the possibility of transferring syphilis by vaccination was entirely done away with." Since 1917 the United States Army has vaccinated approximately 4,700,000 members of its personnel and the United States Navy, 950,000 of its personnel. Of these 5,650,000 persons not one had developed syphilis or a suspicion thereof from vaccination. During this same period the United States Public Health Service had vaccinated 2,918,748 persons in its quarantine, immigration and hospital work, and had never heard of a single complaint concerning syphilis.

During the past ten years more than 2,000,000 persons, including school children have been vaccinated by state and local authorities in coöperation with the United States Public Health Service. Of this grand total of over 10,000,000 vaccinations, not one of the surgeons-general had ever received an allegation or a statement charging that any individual had contracted syphilis as a result of vaccination.

The Relation of Vaccination to Tuberculosis.—Whether or not it is possible to transmit tuberculosis in vaccine lymph is an undetermined question. Toussaint[2] claims to have successfully inoculated rabbits and a pig with tuberculosis with lymph taken from a vaccine vesicle induced upon the vulva of a tuberculous cow. On the other hand, Josserand[3] injected lymph taken from vaccine vesicles in tuber-

[1] Public Health Reports, March 4, 1926.

[2] French Academy of Sciences, August 8, 1881, quoted by Acland: Allbutt's System of Medicine, p. 619.

[3] Quoted by Acland: Contribution a l'étude des contamination vaccinales, Lyons, 1884, p. 30.

culous individuals into the peritoneal cavity, under the skin and into the anterior chamber of the eye in 47 animals. Postmortem examinations gave absolutely negative results in 43 of these and in no animal was there conclusive evidence of tuberculosis.

The danger of conveying tuberculosis in bovine lymph is almost inappreciable. The virus is obtained from calves, and it is pretty well established that calves are but rarely the subjects of tuberculosis. It is stated by Fürst, on the authority of Pfeiffer, that but 1 case of tuberculosis was found among 34,400 calves under four months of age.[1] The statistics of the abattoirs of Augsburg and Münich corroborate the above figures; only 1 tuberculous calf was discovered at Augsburg among 22,230 slaughtered and a smaller percentage at Münich.[2]

Furthermore, in well-regulated vaccine establishments calves are subjected to the tuberculin test before vaccination, and are autopsied before the lymph is distributed for use. Even though it were possible, despite these precautions, for tubercle bacilli to get into the lymph, they would perish if the lymph were glycerinated. Copeman,[3] speaking of glycerinated lymph, says: "The tubercle bacillus is effectually destroyed even when large quantities of virulent cultures have been purposely added to the lymph."

Bollinger, Heron and Acland all seriously doubt whether tuberculosis has ever been transmitted by vaccination.

Postvaccinal Lupus Vulgaris.—Cases of lupus occurring in and around vaccination scars have been reported by Lenander, Besnier,[4] Perry,[5] Little,[6] Colcott Fox, Acland,[7] Stelwagon[8] and others. Most of these observers saw the lupus years after the vaccination had been performed. Fox saw a case of lupus begin in a vaccination scar shortly after the sore had healed. The child subsequently developed a disseminated lupus, subperiosteal tuberculous nodules and pulmonary phthisis. It is highly probable that this child was already tuberculous, as another child in the family had previously died of this disease. Stelwagon saw a palm-sized patch of lupus on the arm in a girl aged ten or twelve years after a vaccination which was said to have been immediately followed by the development of the lupus, the history being given by a physician, the brother of the patient. All that can be stated as regards the relationship of vaccination to lupus is that vaccination may in rare cases in tuberculous individuals stimulate the appearance of a lupus at the site of vaccination. That lupus should occasionally choose a vaccination scar for its seat is no proof that it was caused by vaccination.

[1] Fürst, quoted by Acland: Die Pathologie der Schutz-Pocken-Impfung, Berlin, 1896, p. 112, par. 431.
[2] Strauss, quoted by Acland: Gaz. hebd. de méd. et de chir., 1885, p. 143.
[3] Vaccination, its Natural History and Pathology, London, 1899, p. 181.
[4] Ann. de dermat. et de syph., 1889, p. 576.
[5] Brit. Jour. Dermat., 1898, p. 196.
[6] Ibid., 1900, p. 60.
[7] Loc. cit.
[8] Jour. Am. Med. Assn., November 22, 1902.

Vaccination and Leprosy.—Since the general adoption of bovine lymph for vaccination, the question of the invaccination of leprosy has resolved itself into one of academic and retrospective interest. It is well, however, for physicians in leprous countries, if required by unusual circumstances to employ humanized lymph, to remember that leprosy has probably in isolated instances been conveyed by vaccination. Gairdner,[1] Daubler[2] and Hillis have each recorded instances of vaccinal leprosy, although some doubt attaches to all of these cases.

Beavan Rake and Buckmaster, who have given this matter much study, believe "that the alleged cases of transmission of leprosy by vaccination are open to serious doubt." Hansen,[3] of Bergen, in 1890, made extensive inquiry by circular to all of the physicians of Norway as to the occurrence of vaccination leprosy. In not a single case was there any ground to suspect such an origin. This statement is of especial importance inasmuch as there existed much leprosy in Norway, and vaccination was practised extensively in that country.

It is true that lepra bacilli have occasionally been found in vaccine lymph in vesicles raised upon leprous skin, but, as Beavan Rake properly states, no responsible person would think of vaccinating a leper in an affected part and using such lymph for further vaccinations.

Eczema Following Vaccination.—Vaccination may now and then induce the appearance of an eczema in a child predisposed to the disease, just as an attack of measles, scarlet fever or simple teething may act as an exciting cause. Eczema is an extremely common disease among infants and young children, and is particularly referable to faulty feeding and digestive disturbances. Of 600 cases of eczema under the care of Dr. T. Colcott Fox, 249, or 41.5 per cent, were seen before the end of the first year; in 40 of these eczema was known to have appeared before vaccination. Doubtless if these had appeared after vaccination the latter would have been viewed as a probable etiological factor.

Crocker[4] says: "In no case can vaccination be held responsible where the vaccinia pustule has completely healed before eczema appears."

Eczematous children, if in good health otherwise, may usually be vaccinated without any aggravation of the existing cutaneous disease. Van Harlingen[5] carefully studied the influence of vaccination on previously existing skin diseases. He writes: "During the smallpox epidemic in 1872 I observed all cases of skin disease coming under my notice in which vaccination had been practised. In a few some aggravation of the symptoms followed; in others an apparent improvement took place. But in the great majority of cases vaccination did not appear to exercise any influence whatever on the course of the

[1] A Remarkable Experience Concerning Leprosy, Brit. Med. Jour., 1887, i, 1269.
[2] Monatsh. f. prakt. Derm., 1889, p. 123.
[3] Mentioned by Acland (Allbutt's System of Medicine, p. 625).
[4] Diseases of the Skin, p. 324.
[5] Remarks on Vaccination, in Relation to Skin Diseases and Eruptions Following Vaccination, Philadelphia Med. Jour., 1902, p. 184.

more common diseases of the skin coming under my observation." We have from time to time vaccinated persons with eczema and other cutaneous diseases without any injury whatsoever. On the other hand, vaccination has on a number of occasions been followed by improvement and even cure of eczemas. Stelwagon[1] says: "I have noted in several instances that amelioration followed vaccination and in one instance, in a chronic case, a disappearance of the eczema." Duhring, Tait and others have testified to the occasional curative influence of vaccination on eczema.

While we would not elect to perform vaccination upon a child suffering from eczema, we should not consider the latter condition a sufficient contraindication if smallpox were epidemically prevalent.

Bullous Eruptions (*Dermatitis Bullosa; Dermatitis Herpetiformis; Acute Pemphigus*).—In relatively rare instances vesico-bullous eruptions variously designated as pemphigus, bullous dermatitis and dermatitis herpetiformis (Duhring's disease) have followed vaccination. While we have no proof positive of a causative relationship between vaccinia and these eruptions, they have now been reported by careful observers in a sufficient number of instances to warrant the assumption that the antecedent vaccination has been of some etiological moment.

Pusey[2] reported a case of this character under the title of dermatitis herpetiformis, in which the lesions were vesico-bullous and erythematous, followed by pigmentation.

Dyer[3] reported 2 similar cases under the same title after vaccination. One case occurred three weeks after vaccination and 1 several (?) weeks thereafter.

Bowen[4] has placed on record a series of 6 cases of bullous dermatitis resembling dermatitis herpetiformis following vaccination. In 3 of the cases the eruption is stated to have made its appearance within two weeks after vaccination, in 1 within a week, while in 2 it did not show itself until after the lapse of a month. Corlett exhibits two photographs of postvaccinal bullous dermatitis in his work on the acute infectious exanthemata. Stelwagon[5] saw within one year 3 cases of bullous eruption after vaccination, 2 of which he regarded as *acute pemphigus* and 1 as a persistent bullous erythema multiforme or dermatitis herpetiformis. In these cases the vaccination was what is usually described as a "good take," but was somewhat slow in healing, the crust remaining adherent a long time. The eruption appeared from two to four weeks after vaccination, and had persisted at the time they were reported three, four and eight months, respectively.

Sequeira[6] showed to the Dermatological Society of London in 1902 a case of *pemphigus* in a man, aged thirty-nine years, the eruption

[1] Vaccinal Eruptions, Jour. Am. Med. Assn., November 22, 1902.
[2] Jour. Cutan. and Genito-urin. Dis.; November 22, 1902.
[3] St. Louis Med. Gaz., 1898.
[4] Jour. Cutan. and Genito-urin. Dis., September, 1901, p. 401.
[5] Jour. Am. Med. Assn., November 22, 1902.
[6] Brit. Dermat. Jour., May, 1902, p. 174.

appearing three weeks after a revaccination. Three vaccine insertions were made, and the first bleb is alleged to have developed at the site of one of these. This was followed in several weeks by bullæ on the arms and later on the thighs. Cultures from the early blebs were sterile and inoculations of this fluid into animals were negative.

In all of the above cases save the last, the patients were children under twelve years of age. The eruption usually appeared from two to three weeks after vaccination, and in no case after six weeks. In most cases the eruption was extensive and of long duration, with marked tendency to relapse. Some of the cases were cured at the end of three or six months, but some persisted much longer. Pusey's case continued to have relapses for four and a half years.

A remarkable series of bullous eruptions occurring after vaccination is reported by Howe,[1] of Boston. Ten cases are referred to, all but one occurring in persons who had been recently vaccinated. The skin lesions began on an average of five weeks after vaccination; the longest time elapsing between vaccination and the appearance of the eruption was sixteen weeks and the shortest period three weeks.

All of the patients were adults, the ages varying from twenty-one to fifty-two years. Six of the 10 cases proved fatal; the average duration until recovery or death occurred was six weeks.

It will be seen that these cases present points of variation from the cases described by Bowen. The interval between vaccination and the appearance of the eruption in Bowen's cases was about two and a half weeks; in Howe's cases it was double this period. Bowen's cases occurred in children; none of them were fatal and the trunk was, as a rule, free of eruption, which was not true in the cases described by Howe.

Howe was inclined to attribute the eruptions to infectious material introduced at the time of or after vaccination. The cases occurred at a time when smallpox was prevalent in epidemic form and when thousands of vaccinations were being performed.

While these eruptions, when compared with the number of vaccinations performed, are extremely rare, no effort should be spared to determine their cause with a view to their future avoidance. It is possible that they are manifestations of an extraneous infection through the vaccine wound. In this connection the investigations of Pernet and Bulloch[2] in the causation of acute pemphigus are of interest. These writers reported and analyzed 8 cases of acute pemphigus in butchers; 6 of the cases proved fatal in from twenty-four hours to eighteen days. Three patients gave histories of wounds which continued to suppurate up to the time of the pemphigus outbreak. The period of incubation would appear to be very long if the disease arose from an infection, as is suggested. In the 3 cases referred to the wound antedated the eruption three months, two months and five weeks,

[1] Cases of Bullous Dermatitis Following Vaccination, Jour. Cutan. Dis., 1903, p. 254.
[2] Brit. Jour. Dermat., 1896, pp. 157 and 205.

respectively. Special interest attaches to one case, in which the patient is alleged to have inoculated himself by contact with a bullous eruption on the udders of a cow.

Psoriasis.—Psoriasis is known to have made its first appearance at the point of vaccination, and also as a generalized outbreak after vaccinia. No one, however, who is at all familiar with this disease, would look upon vaccination as a cause of psoriasis. It may simply determine the time of outbreak in an individual predisposed to this common skin affection; it is quite possible that those persons who developed psoriasis after vaccination would not have been attacked with this disease until a later period. The occurrence of postvaccinal outbreaks of psoriasis has been noted by Klamann,[1] 1 case; Campbell,[2] 1 case; Rohe,[3] 2 acute general cases of psoriasis after vaccination; Piffard,[4] 1 case; Wood,[5] 2 cases; Hyde,[6] 1 case; Gaskoin,[7] 5 cases; Chambard,[8] 1 case; Rioblanc,[9] 1 case.

Furunculosis.—Crops of boils have occasionally been observed during the course of and following vaccination. The complication is usually a trivial one, the furuncles disappearing in a short time. Sinigar[10] met with 21 cases of furuncles among 1160 vaccinations in a large institution. The boils developed, as a rule, late in the course of the vaccinia. One case appeared on the tenth day, 1 on the sixteenth, 4 on the twenty-second, 1 on the twenty-fifth, 2 on the twenty-seventh, 2 on the twenty-eighth, 4 on the twenty-ninth, 3 on the thirtieth and 3 on the thirty-fifth day after vaccination. As bearing on the cause of this complication, it is interesting to note that 13 of these cases developed among epileptics, who, as Sinigar remarks, include some of the dirtiest and most troublesome patients in the asylum.

Alleged Chronic Effects of Vaccination.—Certain opponents of vaccination have made allusions from time to time to insidious, chronic and injurious effects of vaccination upon the system. These are gratuitous statements without any basis in fact.

Leicester, England, has been heralded by the opponents of vaccination as the most unvaccinated city in the United Kingdom; the general death-rate was pointed to with pride, the low figure being regarded as due to the abandonment of vaccination. In 1909, a year which represents an average, Leicester, with a population of 244,255, had a general death-rate of 12.9 per 1000 of population. Unfortunately for this argument, there are a number of German cities of similar population which have a lower general death-rate and in which vaccination in infancy and revaccination at the age of twelve years are rigorously enforced.

[1] Jahrb. f. Kinderheilk., 1897, **4**, 371.
[2] Arch. f. Derm., 1877, p. 311.
[3] Jour. Cutan. and Genito-urin. Dis., 1882–1883, p. 11.
[4] Ibid., p. 119.
[5] Ibid., p. 161.
[6] Ibid., p. 14.
[7] On Psoriasis or Lepra, 1875, p. 49.
[8] Ann. de derm., 1895, p. 498.
[9] Ibid., p. 880.
[10] Vaccinal Complications, Lancet, 1902.

Year.	Town.	Population.	Death-rate per 1000 of population.
1909	Rixdorf	213,532	11.3
1909	Schoneburg	164,019	11.3
1909	Charlottenburg	276,300	11.8
1909	Barmen	162,100	12.6
1909	Elberfeld	169,100	12.6
1909	Cassel	157,900	12.7

When the general vaccination and revaccination law went into effect in Germany in 1875, the general death-rate of the country was 29.3. In 1909 it was 18.1.

Other statistical evidence might be adduced to show the fallacy of the contention referred to, but it would subserve no useful purpose.

HISTOLOGY OF THE VACCINE LESION.

Interest in the histological changes in vaccination lesions has been primarily stimulated by a search for the causative organism and on the assumption that the vira of variola and vaccinia possess a peculiar affinity not only for skin tissue as a whole, but likewise for that portion derived from epiblast. But more recent work has shown that in vaccinia a potent virus may be recovered from various organs, indicating that we have to deal with a virus which, though finding in the skin a seat of predilection for proliferative activity, is yet widely distributed throughout the body.

Copeman and Mann[1] as well as Councilman and his colleagues[2] have emphasized the changes occurring in the epiblast and have shown that the vaccine lesion passes through three more or less defined stages—namely, papule, vesicle and pustule—just as does the characteristic lesion of smallpox. In both diseases the *papule* results from inflammatory changes which are most pronounced in the epithelial cells of the mucous layer of the epidermis. Through certain degenerative processes, the most conspicuous of which are cell liquefaction and intercellular edema, the papule becomes converted into a vesicle.

The vesicle is made up of numerous loculi or compartments which are formed by the spinning out of elongated epithelial cells. The more pronounced swelling and vacuolation of the cells upon the advancing edge of the vesicle leads to greater bulging upon the periphery, giving rise to the *umbilication*. The process is identical in vaccine and variolous vesicles.

At a quite early stage an outpouring of leukocytes occurs toward the site of injury. In the course of time each bloodvessel is surrounded by a mass of leukocytes which rapidly increase and convert the originally transparent fluid of the vesicle into a purulent fluid, thus giving rise to the *pustule*.

[1] Twenty-eighth Ann. Rep. Loc. Gov. Board, London, 1899, p. 505.
[2] Jour. Med. Res., 1903, **9**, 372.

The rupture of the epithelial trabeculæ or partitions converts the multilocular pock into a unilocular one. The fluid now gradually becomes inspissated and with the necrosed remains of epithelial cells dries into a *crust*. Cicatrization and healing go on beneath the crust; the depth of the resulting scar depends upon the extent of destruction of the true skin.

Ledingham,[1] however, believes that the lesion is essentially of the order of an acute infective granuloma in which the reticulo-endothelial system is primarily and dominantly involved. He found no evidence that vaccinal virus possesses an elective affinity for epiblastic tissue, but rather that precisely similar tissue responses occur when the virus is introduced into tissues remote from epiblast, such as the subcutis, the peritoneum and the spleen.

Tyzzer[2] made a careful experimental study of vaccination and variolation lesions in animals, particularly with reference to the presence of Guarnieri's bodies. He successfully inoculated the corneas of 25 rabbits with vaccine lymph, and the corneas of 20 rabbits with variolous lymph. In addition a number of calves were vaccinated, some upon the cornea and others upon different parts of the cutaneous and mucous surfaces.

He interprets the cycle of development of the *cytorrhyctes variolæ* in vaccinia as follows:

Infection.—Epithelial cells are invaded by small forms in which it is difficult to distinguish structure. These small forms are found between cells and in various parts of the cytoplasm, but after their entrance into the cell they take a position near the nucleus. *Growth:* After becoming located near the nucleus they become larger, and with this growth the character of their structure becomes apparent. They then consist of a reticular protoplasm in which is a clear spot containing a mass of basic staining material. Although it is impossible to distinguish a nuclear membrane bounding this clear spot, it seems probable that this clear spot with the granules in it is the chromatin of the organism. The organism is situated in a space in the cell, generally many times its own volume. This space is usually continuous with or is a part of the perinuclear space. *Division of the nuclear material:* Certain forms in which the chromatin mass is irregular, precede those in which the chromatin is divided. In the latter the chromatin granules may be few or numerous. The chromatin granules later take a peripheral position, where they then form the centers of minute masses which bulge from the surface. *Multiplication:* These small masses, becoming free, are found in the space occupied by the segmenting form and in the cytoplasm of the same cell. They constitute the small forms described as the first of the series. They now scatter and penetrate neighboring cells. The invasion of the surrounding normal cells by the small forms resulting from this multiplicative process constitutes

[1] Brit. Jour. Exper. Path., 1924, **5**, 332.

[2] The Etiology and Pathology of Vaccinia, Jour. Med. Res., February, 1904.

auto-infection, and by it the process extends. The immediate effect of the parasite is to cause an increase in size of the epithelial cells. This increase in cell volume is accompanied in the corneal lesion by proliferation. The exudation which usually accompanies the lesions is secondary to the degeneration of the epithelium. Tyzzer states that he is "fully convinced that the vaccine body is an organism and represents the etiological agent in this disease."

THE BLOOD IN VACCINIA.

There is a constant leukocytosis during vaccination, the leukocytosis appearing in two waves, according to Sobotka.[1] The primary one (varying from 12,000 to 2,000) is observed from the third to the seventh day, and a secondary wave (10,000 to 17,500) from the tenth to the twelfth day.

Billings[2] states that no changes are exerted upon the hemoglobin or red cells by vaccination, but a definite leukocytosis is produced. The counts average about 15,000 leukocytes per cubic millimeter. The maximum of the leukocytosis is reached during the height of pustulation of the vaccine lesion, after which a gradual diminution in the white cells take place.

[1] Ztschr. f. Heilk., 1893, **14**, 349.
[2] Med. News, 1898, **73**, 301.

CHAPTER II.

THE RELATIONSHIP OF COWPOX OR VACCINIA TO SMALLPOX.

It has taken almost a century of experimentation to prove the truth of the statements made by Jenner in his first publication, that smallpox and cowpox were modifications of the same disease. What a tribute to the intuitive discernment of this great man!

The experiments which have led to the general acceptance of this view have been in the direction of the conversion of smallpox into vaccine by variolation of the cow. It is impossible to produce in the cow a generalized eruption similar to the smallpox eruption in man; it is, moreover, impossible to intensify the virulence of cowpox and convert it into smallpox, but it is possible to convert the virus of human smallpox into vaccine virus by passage through the bovine species.

When reaction results from the insertion of variolous material into the cow the local effects vary somewhat. There may be directly produced a typical vaccine vesicle, or, as occurs in most instances, a papule or inflammatory induration which on further inoculation yields a vaccine vesicle. We are thus forced to the conclusion that *smallpox is converted into cowpox by passage through the tissues of the bovine species.* The transformation is at times sudden and complete, at other times gradual and incomplete and sometimes fails altogether. The circumstances which favor such a conversion are but little understood, although it would appear that the youth of the inoculated animal is a factor. The best results have been obtained with calves not over three or four months old.

That the transformation of the smallpox into the vaccine virus is frequently a gradual process which is not completed in the first bovine inoculation has been on more than one occasion unfortunately proven by the transference of true smallpox to persons who were vaccinated with material taken from the first cow.

That such infections are not the result of inoculation with the unchanged variolous material originally introduced into the cow is evidenced by the fact that smallpox has been conveyed to the human subject from a papule of the second remove. (Lyons Commission.)

These deplorable accidents have directed attention to the unwisdom of using material of the first or second bovine generation, and emphasize the importance of passing the variolous virus through four or five or more animals before employing it upon man.

The demonstration of the fact that vaccine virus may be produced from a variolous source is of great importance. It is readily seen that an epidemic of smallpox occurring in some inaccessible country, where active vaccine lymph could not be obtained, could be made to supply the material for its own suppression.

The proof of the common ancestry of vaccinia and variola refutes the theoretical arguments advanced by Crookshank and others against the protective influence of vaccination. These writers have attempted to fortify their belief in the inefficacy of vaccination by assuming the duality of these two affections, the opinion being maintained that an attack of disease could only afford protection against the same disease. The premise being false, the entire inference falls to the ground.

Modern bacteriological research strongly supports the empiric discovery of Jenner. Pasteur and others have shown that it is quite possible, by the use of an attenuated virus, to produce a mild attack of an infectious disease and thus protect against a more severe type of the same infection.

That vaccinia and variola are in *essence* the same disease is scarcely to be doubted. The passage of smallpox matter through the comparatively insusceptible tissues of the bovine species attenuates the virus to such an extent that it is permanently robbed of the virulence which it once possessed. Instead of producing a dangerous and contagious disease, it gives rise to an innocent affection capable of transmission only by inoculation, and having the beneficent property of protecting against the original disease which gave it birth. Shakespeare might well have had vaccination in mind when he wrote in *Romeo and Juliet:*

> "Take thou some new infection to the eye,
> And the rank poison of the old will die."

Whether smallpox is a cowpox of exalted virulence or cowpox an attenuated smallpox remains apparently unsolvable. Copeman is inclined to support the view championed by Jenner. He says:[1] "The artificially inoculated form of cowpox which we term vaccinia is nothing more nor less than variola modified by transmission through the bovine animal. Perhaps the most reasonable interpretation of such results may be that smallpox and vaccinia are both of them descended from a common stock—from an ancestor, for instance, which resembled vaccinia far more than it resembled smallpox. It is conceivable, indeed, that the seeming vaccinia, obtained in the calf by inoculation of smallpox matter into that animal may after all be but a reversion to an antecedent type."

In Germany most of the vaccine virus in use has been prepared through variolation of the calf.

Sources of Vaccine Virus.—The virus first employed by Jenner in 1798 was taken from the hand of a dairy maid who had accidentlly contracted cowpox from the udders of a milch cow. From the vac-

[1] Vaccination, London, 1899, p. 64.

cination sore on her hand, a young lad, James Phipps, was inoculated, or, as we would now phrase it, vaccinated upon the arm. A number of children was subsequently vaccinated one from the other. This strain of virus subsequently died out.

Vaccination was later carried out with virus from cases of natural cowpox discovered by various observers. Woodville and Pearson, of England, Sacco, of Italy, and many others found new sources of vaccine lymph in cases of so-called spontaneous cowpox in various countries.

A famous strain of lymph was derived in 1836 from a case of natural cowpox at Passy, in the environs of Paris. The lymph was most assiduously studied by Bousquet, who compared the resulting vaccinations with those produced by the older strain.

In 1836, Estlin, of Bristol, put into circulation a lymph derived from a Gloucestershire farm, which was later extensively employed.

In 1841 Ceely stated that he had experimented with lymph from more than fifteen sources, six of which represented cases of natural cowpox.

In 1866 a valuable strain of lymph was developed from a case of natural cowpox occurring in Beaugency, France. This stock was cultivated by Professor Depaul. It was from this source that Martin, of Boston, obtained lymph with which he inaugurated animal vaccination in America in 1870.

In 1881, Martin, of Boston, observed a case of spontaneous cowpox at Cohasset, a small town in Massachusetts. The Cohasset and Beaugency stocks were for a time propagated separately in this country, but subsequently were mixed.

In 1885, Alexander, of Marietta, Penna., found a case of so-called natural cowpox, the virus from which was successfully transmitted through over 2000 calves. This virus is said to be used at the present time.

The lymph stock in use in 1905, at the Government Animal Vaccinal Establishment of London, was originally obtained on November 26, 1881, at a farm in Laforet, near Bordeaux, France.

Vaccine virus can be produced by the successive inoculation of calves with smallpox lymph. The virus is robbed of its contagious properties by this process of transmutation. Successful experiments were carried out by Thiele, of England (1838), Ceely, of England (1840), Badcock, of England (between 1840 and 1860), Voigt, of Germany (1881), Haccius and Eternod, of Switzerland (1890), King, of India (1891), Simpson (1892) and Hime (1892). Within more recent years more successful conversion of smallpox into vaccine virus has been achieved by Fisher, Voigt, Copeman, Freyer and others.

The use of vaccine virus of *variolous* origin, or variola vaccine, as it is called, is officially sanctioned by the German Government and such virus has been and is extensively employed throughout the German Empire.

For many years vaccine virus was continued by direct arm-to-arm vaccination and later by the use of an emulsion made from the dried vaccine crust. This virus is referred to as *long humanized virus.*

In 1891, Copeman, of England, advocated the use of *glycerinized virus;* this has come into general use and is almost universally employed at the present day. The addition of a proper amount of glycerin to the virus gradually destroys the life or the pathogenicity of the extraneous germs that may have gained entrance to the virus. The use of glycerinated lymph is one of the most important advances that has been made since the discovery of vaccination.

It is evident from what has been said thus far that vaccine virus may be derived from natural cowpox, which is believed to be due to an accidental smallpox infection of the cow, or from variola vaccine which is produced by purposeful variolation of the bovine species. This virus may be transmitted through a successive series of human beings, as with the use of the long humanized virus (now obsolete and abandoned in this and most other countries), or it may be transmitted through successive generations of calves. The latter is the virus generally employed.

Opponents of vaccination have asserted that vaccine virus is an unknown substance without constancy in composition and derived from diverse affections. No scientific evidence, however, is at hand to prove this assertion.

That vaccine lymph is a specific virus, producing definite and well known effects, is demonstrated by experienced vaccine propagators. Laboratory research on monkeys conclusively proves that vaccine virus protects against a subsequent inoculation with either vaccine or smallpox virus.

In the human subject vaccinia runs a definite and characteristic course, passing successively through the stages of papule, vesicle and pustule; the acme of the affection is reached about the eighth day, when an areola or reddish inflammation is seen about the pustule; after this the inflammatory process gradually subsides, leaving a brownish-red firm crust at the site of vaccination. After the detachment of the crust a more or less characteristic scar is left.

The affection induced by vaccinia is just as specific and characteristic as is measles or smallpox.

Definition of Vaccine Virus.—An attempt has been made to discredit vaccination because of the alleged inability to scientifically define vaccine virus. The germ which produces vaccinia is not definitely established, although microscopic bodies are found both in vaccinia and variola (and in these affections alone) which are believed by many to be the parasitic cause of both. Despite the absence of proof in this connection, a satisfactory definition of vaccine virus, based upon its physical and biological properties, can be given.

Vaccine virus is a slightly alkaline fluid coming from the serum or plasma of the blood, containing epithelial skin cells and their débris,

leukocytes (white blood cells) and occasionally red blood cells, in addition to the specific, though as yet not definitely proven parasitic microörganism. The vaccine virus is developed at the site of inoculation with either cowpox or variola vaccine material, the lesion passing successively through the stages of papule, vesicle and pustule and crust, the acme of the process being reached at the end of eight days. Inoculation with vaccine virus protects the subject for a period of years against subsequent infection with vaccinia or with smallpox. Under the microscope, characteristic bodies, known as Guarnieri bodies, are found.

The seed virus employed by vaccine propagators in this country at the present time has been in large part secured from the vaccine establishments abroad, from Germany, Switzerland, France and other countries. The American propagators do not, as a rule, know the original source of the virus, which may date back for decades; the information would be interesting, but unessential, inasmuch as the properties of the lymph are well known to the foreign and to the American propagators.

We are conscious of a reassuring sense of security in the knowledge that reliable vaccine lymph can be produced by the inoculation of variolous material into a succession of bovine animals, for if existing strains of lymph are lost or become too much attenuated, we have at hand a means of replenishing the prophylactic virus.

Animal Vaccination.—By the term animal vaccination is meant the propagation of lymph through successive series of calves or heifers, the original virus being derived *ab initio* from a case of spontaneous cowpox.

In 1810 a Neapolitan physician, Galbiati by name, published an article advocating animal vaccination. He had employed this method for some seven years, believing that it ensured greater vigor and purity of the lymph. Galbiati seems to have espoused this procedure because of the occasional transmission of syphilis by arm-to-arm vaccination. His disciple and successor, Negri (to whom Ballard gives credit for the origin and introduction of animal vaccination), continued the propagation of lymph from animal to animal, and successfully brought the practice into general favor. The lymph which he employed at first (in 1842) appears to have been of human origin, but subsequently he obtained material from a case of natural cowpox in Calabria. Palasciano, a townsman of Negri and a strong advocate of animal vaccination, disseminated knowledge on this subject throughout Europe, by an address before the Medical Congress of Lyons. A young French physician, Lanoix, one of those present, became greatly interested in the subject and subsequently went to Naples to study animal vaccination under Negri. In 1864 he returned to Paris with a heifer which had been vaccinated at Naples. Chauveau and Diday were permitted to take some lymph from this animal at the Lyons railway station. Lanoix proceeded to Paris and in company with Chambon established a private institution for the propagation of animal lymph. About

this time natural cowpox was discovered at Beaugency, and Depaul had an opportunity of employing lymph from this source. It is said that this lymph stock was lost during the siege of Paris in the Franco-Prussian War, and that the only extant derivative from this source is that sent to America.

From Paris the practice of animal vaccination spread to Belgium through the efforts of Warlomont, who obtained some Neapolitan lymph from Lanoix. He later, in 1868, discovered a case of spontaneous cowpox at Esneux (Liège).

Through private enterprise animal vaccine establishments were organized in the various European capitals. The commercial spirit rendered a real service to humanitarian science.

Pissin opened up such an animal vaccine institution in Berlin, and Vienna soon had a similarly equipped establishment. Haccius, in 1882, founded the "Institute Vaccinale Suisse," which received a certain recognition at the hands of the Swiss government. Paris opened an "Institut de Vaccine Animale," which under the direction of Chambon and St. Yves Ménard, supplied the municipality with all the lymph required for public vaccinations.

In Germany all or nearly all of the vaccine establishments are under governmental control and supervision.

England, in 1881, authorized the founding of the Government Animal Vaccine Establishment in Lamb's Conduit Street, and the use of animal lymph has now practically superseded arm-to-arm vaccination.

To Dr. H. A. Martin, of Boston, belongs the credit of introducing animal vaccination into the United States. In 1870 he sent a special agent to France, who returned with an abundant supply of Beaugency lymph. Having secured a herd of young, healthy animals, he at once began the propagation of animal lymph. He and his son subsequently discovered a case of spontaneous cowpox in Cohasset, Mass.

Animal lymph appears to give a much larger percentage of successful revaccinations than long humanized virus. Martin says: "The number of those who, in revaccination with the old, long humanized virus (not that of early human removes) experience vaccinal effect may be stated at the outside at 35 per cent. The number of those revaccinated with equal care and repetition with animal virus and virus of very early human removes, I affirm to be a fraction over 80 per cent—a difference of 45 per cent; this 45 per cent I firmly believe to approximately represent the number of those insensible to the enfeebled influence of long humanized virus, but sensible to the intense contagium of variola just in the same degree as sensible to the intense power of bovine virus and that of the early human removes from it."

Veterinary Inspection of Calves Used in the Propagation of Vaccine and the Disposal of the Carcasses Thereof.—An Act of Congress, approved July 1, 1902, regulating the manufacturing and interstate sale of viruses, serums and analogous products, makes specific provision for the veterinary inspection of calves before vaccination.

The clause of the Act referring to examination by a veterinary physician, is as follows: "Animals used for propagating vaccine virus must be under daily veterinary inspection for not less than seven days, immediately before they are vaccinated. Only healthy animals free from communicable disease shall be used for this purpose."

According to Act of Congress: "The practice of renting animals for the purpose of propagating vaccine virus, and returning the animals to the market, shall be discontinued." Medical representatives of the two vaccine farms located in Pennsylvania have testified that the meat of the vaccinated calves used by them was not subsequently placed on the market. It was used as fertilizing material or for laboratory purposes. It was testified, however, that such meat is employed as food in England and in Germany.

The Examination of Vaccine Virus and the Sanitary Condition of Vaccine Establishments, Etc.—Under the Federal Law of July 1, 1902, and the regulations framed thereunder, all of the firms manufacturing vaccine virus are required to be licensed by the Secretary of the Treasury, before they shall sell their products in interstate commerce. There are seven firms engaged in this business in the United States, and all of these firms are licensed and therefore subject to the provisions of the Act of Congress above referred to.

Previous to the licensing of a vaccine establishment it must be inspected by an official of the Public Health Service. The vaccine virus must, furthermore, be examined by the Hygienic Laboratory of the United States Public Health Service. The report of the inspector, together with the report of the examination of the virus, is submitted to the Sanitary Board of the Public Health Service for consideration. The Board considers these two reports, and on these reports bases its recommendations for or against a license of the particular firm making application therefor.

The regulations in regard to the manufacture and interstate sale of vaccine virus are quite strict and comprehensive, looking to the maximum safeguarding of the product manufactured and sold by vaccine propagators. In making inspections of vaccine establishments, the official Inspector of the Public Health Service is required to make his visit unannounced; he makes a thorough inspection of the premises, the appliances, the stables, the warehouses, the methods of preparation of virus and the records kept; he also considers the qualifications of the personnel to properly carry out the Federal regulations. The inspectors are authorized, when they deem it desirable, to interrogate the members or employees of the firm, under oath.

The inspector obtains samples of the vaccine virus at the establishment, going to the refrigerator or storeroom and taking as many samples as he desires. In addition, in order to secure such virus as is sold to the public, he buys the product of the firm in the open market in various sections of the country.

The vaccine virus is rigorously examined by the Hygienic Labora-

tory. Manufacturers are now required to submit large amounts of each lot of vaccine virus, in addition to that purchased in the open market. Vaccine virus is examined daily by a laboratory worker who devotes all of his time to this work.

The Federal regulations require that "each and every lot of vaccine virus shall be examined to determine its freedom from pathogenic microörganisms, and a special examination must be made of each and every lot, to determine the absence of tetanus; detailed and permanent records of these examinations shall be kept by the establishment propagating said virus."

In the vaccine establishments themselves the virus is put through rigorous tests to exclude the presence of any harmful germs. The vaccine virus is injected into susceptible animals and the effect of the injection thoroughly studied before the virus is marketed.

It is required by the Federal regulations that an autopsy be made on each calf after the vaccine virus has been removed. In the event that any communicable disease is found or suspected in the animal the virus may not be placed upon the market, but must be destroyed. Permanent records of each autopsy, in which particular reference shall be made of pathological changes present, shall be kept.

The chief preservative and germicide used in vaccine lymph is glycerin. The amount varies slightly in different establishments. Ordinarily the virus is mixed with six times its weight of a sterilized solution of 50 per cent chemically pure glycerin in distilled water. The glycerin has the property of gradually destroying the extraneous germs which may be present in the lymph.

Comparison of the Course of Vaccinia Produced by Original Cowpox Virus, Long Humanized Virus, and Calf-transmitted Virus, Respectively.—**Original Cowpox Virus.**—The vaccine disease produced by virus from a case of *original cowpox* or from early human removes therefrom lasts from twenty-one to thirty-two days, counting from the insertion of the lymph to the falling of the crust. At the end of the third or beginning of the fourth day papulation occurs; vesiculation takes place at the end of the fifth day, but the vesicle continues to grow until the decline of the areola or even a few days after this. The vesicle has a pearly or slightly bluish tint; it really resembles, as Jenner remarked, "a section of a pearl on a rose leaf." The areola appears first about the end of the ninth or beginning of the tenth day and persists until the twelfth, thirteenth or fourteenth day. Desiccation and formation of the crust are not complete before the sixteenth or seventeenth day; the crust is never spontaneously detached before the twenty-first day and usually not before the twenty-fifth to the twenty-eighth day. Occasionally it will remain upon the vaccine site until the thirtieth or thirty-second day. The crust is round, thick, umbilicated and of a rich brown or mahogany tint.

A very decided febrile reaction attends the rise, development and decline of the areola. This febrile disturbance was considered to be

of great importance by the early vaccinators, especially Jenner, who regarded it as a *sine qua non* of vaccinal impression upon the system, and an indelible characteristic cicatrix remains after the termination of the disease. In the early days it was not at all rare for the vesicle to break down and ulcerate, leading to a spreading and troublesome loss of tissue and occasionally to erysipelatous infection.

Long Humanized Virus.—The most distinguishing characteristic of the vaccinia produced by long humanized virus is the brevity of the course of the disease. The duration varies very much with different lymph stocks. With a virus used by Martin and obtained from Ceely the course of the disease from the time of insertion of the lymph to the spontaneous detachment of the crust was but eleven days; whereas with a lymph of French origin employed by Martin the crust came off from the twenty-first to the twenty-sixth day. Lymph from the National Vaccine Institution of Great Britain ran a course of fourteen days to the falling of the crust. These various "stocks," although propagated for years, preserved their distinctive durations. It was even found, when two different lymphs were inserted, one on one arm and the second on the other, that each strain retained its special features.

In brief, it may be stated that long humanized lymph produces a vaccinia of shorter duration and milder intensity than original and early virus.

Calf-transmitted Virus.—As would be expected the vaccinia resulting from the employment of calf-transmitted lymph closely resembles the disease induced by early human removes from original cowpox, such as were observed by Jenner. With the animal-transmitted virus, however, the reaction is not so violently inflammatory as that which occurred with original cowpox lymph. Ceely, in 1840, stated his belief that the tendency to undesirable intensity in the original cowpox is tempered by successive transmissions through young animals. He inoculated a series of 11 calves and found that the objectionable qualities of the lymph, as determined by human vaccinations, were gradually but progressively eliminated. The animal virus now used usually runs its course from twenty-one to thirty days.

Glycerinated Lymph.—To S. Monckton Copeman[1] belongs the credit of advocating the addition of glycerin as a vaccine purifier, and of establishing the employment of glycerinated lymph upon a scientific basis. Glycerin had previously been used for the purpose of increasing the volume of the lymph and also as a lymph preservative.

As far back as March, 1850, Mr. R. Cheyne[2] advocated (in a letter appearing in the *Medical Times*) the use of fluid lymph to which some glycerin had been added as superior to the dry points. In 1853 he

[1] We desire to acknowledge our indebtedness for much of the material presented in this section to the admirable book of S. Monckton Copeman (Vaccination, its Natural History and Pathology, London, 1899), which we have freely consulted.

[2] Copeman appears to have been unaware of Cheyne's work until a few years ago.

demonstrated to the presidents of the Royal College of Physicians and Surgeons a child whom he had successfully vaccinated with glycerinated lymph prepared six months previously. Cheyne admitted that he was indebted for knowledge of this procedure to the previous publications of Mr. J. Startin, on the *therapeutic uses of glycerin.*

Müller, of Berlin, further demonstrated the fact that vaccine lymph could be considerably increased in quantity by the admixture of glycerin without interfering with its specific activity. He proved that the lymph might be diluted with three times its bulk of glycerin without in any way lessening its potency. It is evident that Müller's chief object was to increase the quantity of available lymph, a matter of much importance during smallpox epidemics, particularly when there was danger of a vaccine famine.

With the same object in view Dr. Stephen Mackenzie, of the London Hospital, during the great smallpox epidemic in 1870–1871, added glycerin to lymph in order to increase the amount just before conducting a large series of vaccinations.

Dr. Warlomont, of Brussels, in 1882, placed upon the market, under English patent, a method of admixture of glycerin with vaccine lymph, but no mention was made of the contained glycerin until some years later.

Copeman, in a paper presented to the International Congress of Hygiene, held in London in 1891, advocated the addition of glycerin to vaccine lymph for the purpose of purifying and preserving it. The method consisted in the "intimate admixture of a given amount of lymph, or rather vesicle pulp, with a sterilized 50 per cent solution of chemically pure glycerin in distilled water, and in subsequent storage of the resultant emulsion in sealed capillary tubes for several weeks."

Copeman had previously endeavored by diverse means to inhibit the growth in vaccine material of the various extraneous organisms, and if possible destroy them without weakening the specific activity of the lymph. These measures failing, he resorted to the addition of glycerin.

Previous to Copeman's experiments there had been no appreciation of the influence of the glycerin as a bacteriological purifier of lymph when the mixture is stored for some time and protected from the access of light and air.

In 1896 the German government appointed a commission presided over by Schmidtmann, and including Koch, Pfeiffer and Frosch, together with the Directors of the Vaccine Institutes of Berlin, Cologne and Stettin, to investigate into the best methods for the collection, preservation, storage, distribution and use of vaccine lymph. The report stated that fresh lymph contained numerous bacteria which diminish progressively under the influence of the glycerin admixture. Streptococci and diphtheria organisms added to the lymph were killed in eleven days and twenty days respectively. These experimenters, as well as Kitasato, in Japan, determined that glycerin with distilled

water could be added to the extent of from fifteen to twenty times the weight of vesicle pulp without destroying the vaccine principle.

Copeman and Blaxall have shown that not only are the ordinary foreign bacteria of fresh lymph destroyed by glycerinization, but that pathogenic organisms such as those of tuberculosis and erysipelas, when added in large number for experimental purposes, also perish.

Copeman sets forth the advantages of glycerinated lymph in the following terms:

"1. By employing the method of glycerination of lymph pulp great increase in quantity can be obtained without any consequent deterioration in quality, the percentage of insertion success following on its use being equal to that obtained with perfectly active fresh lymph.

"2. Glycerinated lymph does not dry up rapidly as does unglycerinated lymph, thus simplifying the process of vaccination.

"3. Glycerinated lymph does not coagulate; so that it never becomes necessary to discard a tube on this account.

"4. *Glycerinated lymph can be produced absolutely free from the various streptococci and staphylococci* which are usually to be found in untreated calf lymph, and which are, under certain circumstances, liable to occasion suppuration.

"5. In like manner the streptococcus of erysipelas, in the event of its having been orginally present in the lymph material, is rapidly killed out by the germicidal action of the glycerin.

"6. The tubercle bacillus is effectually destroyed even when large quantities of virulent cultures have been purposely added to the lymph.

"7. The possibility of inoculation of syphilis is eliminated, as the calf is not subject to this disease.

"8. The necessity for collecting children together, with the attendant risk of spread of infectious diseases, or of transporting a calf from place to place, is obviated, while the danger of 'late' erysipelas in the child is diminished by reason of there being no necessity to open the mature vesicle for the purpose of obtaining lymph.

"9. The bacteriological purity and clinical activity of large quantities of the lymph can be readily tested prior to distribution.

"10. By reason of the possibility of keeping large stocks of glycerinated lymph on hand for considerable periods of time without appreciable deterioration, any sudden demand, such as is likely to arise on the outbreak of epidemic smallpox, can be promptly met.

"11. The expense of producing glycerinated lymph is proportionately small, since the amount obtainable from each calf is enormously increased."

The Preparation of Glycerinated Calf Lymph (Copeman).—"The method best adapted for the production of glycerinated calf lymph which shall be free from all extraneous organisms, of perfect efficacy and yet affording material for the vaccination of many more children than the original unglycerinated calf lymph, is briefly as follows:

"The Preparation of the Calf.—A female calf of suitable age, about from three to six months, should be kept under observation for a week, after which, if found to be quite healthy, it may be removed to the vaccination station. It is there placed on a tilting table, and the lower part of the abdomen, reaching as far forward as the umbilicus, is shaved and thoroughly washed with a solution of carbolic acid and then rinsed with sterile water and dried with soft, sterilized towels.

"Inoculation of the Calf.—With a sterilized, sharp scalpel incisions about 4 inches long and ½ inch apart, parallel to the long axis of the body, are made on this clean-shaven area. The depth of the incision should be such as to pass through the epidermis and to open the rete Malpighii, if possible without drawing blood. As these incisions are made, glycerinated calf lymph, which by examination has been proved to be free from extraneous organisms, is run into them by means of a sterilized blunt instrument, and the point of the scalpel is from time to time dipped into the vaccine emulsion.

Fig. 25.—Belly of heifer, showing one of the approved modern methods of propagating vaccine virus; lesions photographed at the end of five days. (Courtesy of Dr. William F. Elgin.)

"Collection from the Calf.—After five days (one hundred and twenty hours) the vaccinated surface of the calf is first thoroughly washed with warm water and soap, rubbed over it by the clean hand of the operator, and finally the whole area is carefully cleansed with sterile water. The remaining moisture is then removed by sterilized sheets of blotting paper. The vaccinated incisions will now appear

as lines of continuous vesicles raised above the surface, each line separated from its neighbor by about 1 inch of clear skin. Any crusts which appear in the vesicular lines are picked off with a blunt, sterilized instrument. The vesicles and their contents are then removed by means of a sterilized Volkmann spoon, and transferred to a sterilized bottle of known weight. By going over the lines only once with the spoon it is quite easy to remove the whole of the pulp without any admixture of blood. The abraded surface is carefully washed, and may be dusted over with fine oatmeal or starch and boracic powder. Subsequently, the calf is transferred to the slaughter house and the carcass is examined by the veterinary surgeon, who forwards a certificate of its condition. Should this not be satisfactory, the vaccine pulp obtained from the animal is destroyed.

"Preparation and Glycerination of the Lymph Pulp.—The bottle containing the vaccine pulp is taken to the laboratory and the exact weight of the material ascertained. A calf vaccinated in this way will yield from 18 to 24 gm., or even more, of lymph pulp. This material is then thoroughly rubbed up in a sterilized mortar or in a mechanical triturating machine. When it has been brought to a fine state of division it is mixed with six times its weight of a sterilized solution of 50 per cent chemically pure glycerin in distilled water. The resulting emulsion is then transferred to small test-tubes, which are then aseptically sealed and should be stored in a cool place protected from light. When required for distribution it is drawn up into sterilized capillary tubes, which are subsequently sealed in the flame of a spirit lamp.

"Bacteriological Examination of the Lymph Emulsion.—As soon as the vesicular pulp is thoroughly emulsified with the glycerin solution, agar-agar plates are established from it, and after suitable incubation for seven days the colonies that have developed on the plates are counted and examined. Week by week this process is repeated, and invariably the number of colonies diminishes with the age of the emulsion, until at the end of the fourth week after the collection and glycerination of the lymph material the agar-agar plates inoculated at that time show no development of colonies. The lymph is then subjected to further culture experiments, and if these results of freedom from extraneous organisms are confirmed the emulsion is ready for distribution. The elimination of the extraneous organisms in our experiments has occurred with marked regularity at the end of the fourth week. The only exception to this rule arises when the lymph originally contained a considerable number of spores or bacilli of the hay bacillus or Bacillus mesentericus. These organisms are very resistant to the action of glycerin, but if the precautions detailed are carried out in the treatment of the calf their presence may generally be excluded.

"Duration of Activity of Glycerinated Calf Lymph.—This varies in all probability with atmospheric conditions, with the fineness

of division of the vesicle pulp and, above all, with the condition of the calf itself. Some calves yield an excellent lymph, others a poor lymph and the problem is to determine the value of the lymph yielded by any given calf. A lymph which was collected and glycerinated on July 13, 1897, has since been used at intervals of from twenty-four to thirty-two weeks after glycerination for the vaccination of children. During this period 61 children have been vaccinated with this lymph in five places each, with a mean insertion success of 98 per cent. Thus, by the methods described, glycerinated calf lymph can be prepared, which becomes freed from extraneous organisms, is available for a large number of vaccinations, at least 5000 from an average calf, and retains full activity for eight months, and will under favorable circumstances continue to do so in all probability for still longer periods, if necessary."

STATISTICAL EVIDENCE OF THE EFFICACY OF VACCINATION.

Although smallpox dates back many centuries, we have no trustworthy record of the extent of its prevalence before the fifteenth century. About this time it began to be common in Western Europe, increasing during the sixteenth and particularly the seventeenth century, and prevailing still more extensively in the eighteenth.

The beginning of the nineteenth century was characterized by a sudden and striking decrease in the morbidity and mortality of smallpox.

Inasmuch as the announcement of the protective influence of vaccination (1798) and the diffusion of this practice immediately preceded this decline, there is the strongest reason to regard Jenner's epoch-making discovery as the causative influence.

As has been previously shown, smallpox was a great scourge before the days of vaccination. But a small percentage of the population escaped its ravages. It is claimed that in the eighteenth century, according to contemporaneous writers, 95 per cent of the inhabitants of European countries suffered at one time or other from the smallpox. In other words, but 5 persons out of very 100 went through life without being attacked by this dread malady. This is rendered credible when we appreciate the fact that smallpox is among the most contagious of all diseases, and that nearly every human being is highly susceptible to it. Haygarth, who lived in the eighteenth century, stated that the proportion of mankind incapable of infection by smallpox "was observed to amount to 1 in 20;" this would account for the exemption of the 5 per cent referred to.

This author reports an epidemic of smallpox in Chester in 1774, at which time, out of a population of 14,713, 1202 persons took the disease and 202 died. At the termination of the epidemic there were but 1060 persons, or 7 per cent, of the population who had never had smallpox.

In an epidemic of smallpox at Warrington in 1773, in a population of 8000, 211 persons succumbed to the disease. The total deaths during the year from all causes were 473.

In 1722 an epidemic raged in the small English town of Ware, which had a population of 2515. Of this number there were only 914 persons susceptible to smallpox, as 1601 had already had the disease. During the epidemic 612 persons were attacked, leaving but 302 individuals in the entire town who had never had smallpox.

Rapid Decline in Smallpox Mortality After the Introduction of Vaccination.—Inasmuch as accurate records of smallpox mortality were kept in various countries, it is possible to prove by documentary evidence that a striking fall in the number of deaths from this disease occurred shortly after the introduction of vaccination.

Sweden.—Vaccination was introduced into this country in October, 1801. According to the official figures of the Medical College, there were performed 25,000 vaccinations by the year 1805, 23,000 in 1805 and about 19,000 in 1806. Vaccination was made compulsory in 1816. The average death-rates per 1,000,000 of population for the decades from 1774 to 1821 show a decided and progressive decrease in the mortality of smallpox (Fig. 26).

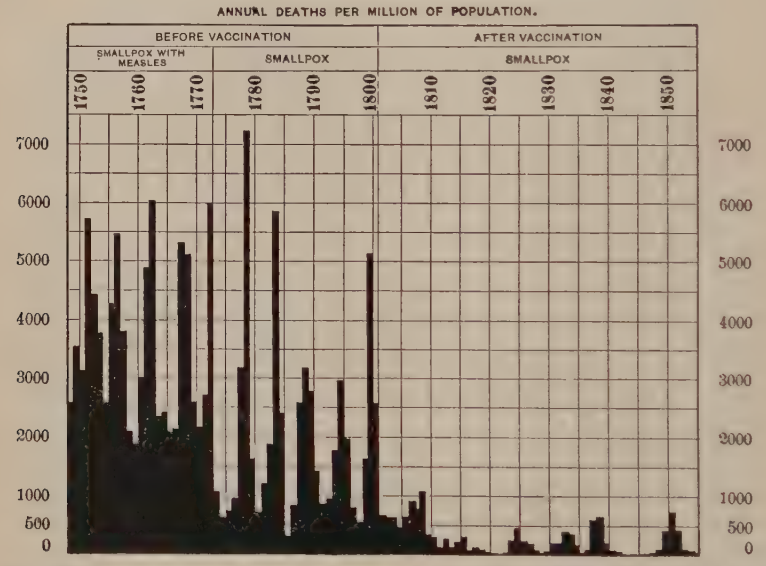


FIG. 26.—Smallpox death-rates for Sweden from 1749 to 1855. (Calculated by Mr. Haile from returns communicated by the Swedish government. Published in papers communicated to the Houses of Parliament, London, 1857.)

AVERAGE YEARLY DEATH-RATES FROM SMALLPOX PER 1,000,000 OF POPULATION FOR DECADES FROM 1774 TO 1821. SWEDEN.

Before vaccination:	
1774–1781 (8 years)	1999
1782–1791	2219
1792–1801	1914
After vaccination:	
1802–1811	623
1812–1821	133

The influence of vaccination in lessening smallpox mortality in Sweden is so clearly shown in the above table as to require no further discussion.

The contrast in smallpox mortality may be expressed in another manner. In the *twenty-eight years before vaccination* in Sweden there died each year from smallpox, out of each 1,000,000 of population, 2050 persons; during the *forty years following vaccination*, out of each 1,000,000 of population the smallpox deaths annually averaged 158.

In Berlin for twenty-four years preceding vaccination the death-rate from smallpox was 3422, and for the first forty years of the vaccination era it was 176.

By the middle of the nineteenth century the fatality of smallpox had been reduced in Copenhagen to one-eleventh of the prevaccination death-rate; in Sweden to a little over one-thirteenth; in Berlin, and in a large part of Austria, one-twentieth; in Westphalia one-twenty-fifth. In the last-named place but 4 persons died about the middle of the century compared to 100 in the prevaccination days.

SMALLPOX DEATHS EACH YEAR FROM THE "BILLS OF MORTALITY," LONDON, 1801 TO 1830.

Before vaccination era.		After vaccination era.	
Decade.	Smallpox deaths.	Decade.	Smallpox deaths.
1761–1770	20,434	1801–1810	12,534
1771–1780	20,923	1811–1820	7,858
1781–1790	17,867	1821–1830	6,990
1791–1800	18,477		

1801–1810.		1811–1820.		1821–1830.		1831–1837.	
1801	1,461	1811	751	1821	508	1831	563
1802	1,597	1812	1287	1822	604	1832	771
1803	1,202	1813	898	1823	774	1833	574
1804	622	1814	638	1824	725	1834	334
1805	1,685	1815	725	1825	1299	1835	863
1806	1,158	1816	653	1826	503	1836	536
1807	1,279	1817	1051	1827	616	1837	217
1808	1,169	1818	421	1828	598		
1809	1,163	1819	712	1829	736		
1810	1,198	1720	722	1830	627		
Smallpox	12,534		7856		6990		3858

The above figures show a decided contrast in smallpox mortality between the decades immediately preceding and following the introduction of vaccination. In the twenty-seven years elapsing from 1811 to 1837 the smallpox deaths exceeded 1000 but three times.

Berlin.—Below are compared the deaths from smallpox per 100,000 *inhabitants* in the prevaccination and postvaccination periods:

	Persons.		Persons.
1758–1762	407	1790–1794	310
1763–1767	364	1795–1799	239
1768–1772	294	1800–1804	261
1773–1784	?	1805–1809	083
1785–1789	360		

(In the first decade of the nineteenth century vaccination was not actively practised in Berlin; it became generally employed in the year 1810.)

	Persons.		Persons.
1810–1814	31	1840–1844	13
1815–1819	40	1845–1849	2
1820–1824	4	1850–1854	5
1825–1829	13	1855–1859	18
1830–1834	19	1860–1864	30
1835–1839	18	1865–1869	26

In the quinquennium 1870–1874 occurred the great pandemic of smallpox which swept the entire civilized world. There died in Berlin during this period, per 100,000 population, a yearly average of 160; this number considerably exceeds all the previous years of this period, but still falls far below the average of the prevaccination years.

From 1795 to 1799, before the days of vaccination, smallpox caused 6.5 per cent of all deaths in Berlin. In the five years following the introduction of vaccination the figures were: 7.5 per cent, 6.4 per cent, 0.7 per cent, 1.3 per cent and 0.2 per cent.[1]

SMALLPOX MORTALITY PER 1,000,000 LIVING, SWEDEN, 1774 TO 1893.

Before vaccination.		Permissive vaccination.		Era of compulsory vaccination, 1817–1893.					
1774	1020	1802	644	1817	96	1845	2	1873	265
1775	631	1803	611	1818	120	1846	1	1874	936
1776	737	1804	605	1819	63	1847	4	1875	484
1777	943	1805	449	1820	55	1848	21	1876	136
1778	3178	1806	613	1821	14	1849	99	1877	79
1779	7196	1807	884	1822	4	1850	395	1878	44
1780	1593	1808	757	1823	15	1851	707	1879	31
1781	699	1809	1007	1824	226	1852	433	1880	38
1782	1165	1810	347	1825	449	1853	78	1881	65
1783	1832	1811	291	1826	223	1854	57	1882	34
1784	5810	1812	167	1827	212	1855	11	1883	27
1785	2361	1813	225	1828	90	1856	14	1884	12
1786	311	1814	126	1829	19	1857	132	1885	0.8
1787	823	1815	191	1830	36	1858	345	1886	0.2
1788	2534	1816	277	1831	211	1859	388	1887	0.6
1789	3137			1832	213	1860	184	1888	1.5
1790	2734			1833	387	1861	49	1889	0.4
1791	1421			1834	352	1862	37	1890	0.2
1792	878			1835	147	1863	76	1891	0.2
1793	942			1836	45	1864	182	1892	0.8
1794	1757			1837	117	1865	323	1893	5
1795	2955			1838	583	1866	292		
1796	1963			1839	621	1867	252		
1797	751			1840	207	1868	342		
1798	585			1841	75	1869	354		
1799	1609			1842	18	1870	183		
1800	5126			1843	3	1871	78		
1801	2563			1844	2	1872	81		
Average,	2045	Average,	480	Average of 77 years, 155					

[1] Denkschrift k. Gesundheitsamt, Berlin.

It is thus seen from the statistics above quoted that after the discovery of vaccination the deaths from smallpox markedly decreased in every country in which this practice was introduced.

Change in the Age Incidence of Smallpox.—In the prevaccination days smallpox was *essentially a disease of children* and, indeed, was designated *Kindspocken* (childpox), or *Kindsblattern*. Owing to the extreme contagiousness and the almost universal susceptibility to smallpox, the vast majority of people contracted the disease in childhood and the adult population being made up largely of survivors was thus immunized.

The conditions in relation to smallpox were much as they are at the present day in regard to measles. Comparatively few adults contract measles because the great bulk of the people pass through the disease in infancy.

As an instance of the incidence of smallpox among children in the prevaccination days, an epidemic occurring in 1795–1796, described by Schwarz,[1] is here referred to. The epidemic occurred in Rawicz, Bojanow and Sarnowo in the Prussian province of Posen. The entire population of the three towns at the beginning of the epidemic was 13,329. Of this number 1252, or 9.4 per cent, were attacked with variola, and 199, or 1.5 per cent of the population and 15.9 per cent of the infected, died. At the end of the epidemic there were only 524 people remaining who were susceptible to the disease.

The almost exclusive mortality of smallpox among infants and children is exemplified in the smallpox statistics of Kilmarnock from 1728 to 1764, a period of thirty-one years. During this time the total deaths were 3860 and the deaths from smallpox 622. There were nine epidemics of smallpox recurring at intervals of about four years. Of *the 622 smallpox deaths, 586 were in children under six years of age;* 27 occurred in persons over the age of six years, and the age of 9 persons was not known.

In Chester, in the epidemic of 1774, all of the smallpox deaths, numbering 202, occurred in children under ten years of age, and one-quarter of them under one year.

In Kilmarnock, of 622 deaths from smallpox between 1728 and 1763, only 7 were of those above ten years.

In 1773 Warrington[2] sustained an epidemic of smallpox which resulted in 211 deaths (population 8000). In 1893 another epidemic occurred which resulted in 62 deaths (population 54,084, of whom 53,645 were vaccinated). The ages of the patients fatally attacked are tabulated on p. 114.

In 1773 *all of the deaths were under ten years,* and nine-tenths were under five years of age.

In 1893 among the vaccinated *not a death occurred under eight years of age;* indeed, not one vaccinated child under eight years of age contracted smallpox.

[1] Quoted by Immerman: Nothnagel's Encyclopedia of Practical Medicine, p. 225.
[2] Quoted by Edwardes: Loc. cit.

SMALLPOX DEATHS.

Age.	1773.	1893. Vaccinated.	1893. Not vaccinated.
Under 1 year	49	0	8 (under 1 month)
1 to 2 years	84	0	1
2 to 3 "	33	0	0
3 to 4 "	18	0	1
4 to 5 "	15	0	1
5 to 6 "	4	0	0
6 to 7 "	2	0	0
7 to 8 "	2	0	0
8 to 9 "	4	1	1
9 to 15 "	0	1	1
15 to 20 "	0	1	2
20 to 30 "	0	10	4
30 to 60 "	0	24	5
Over 60 "	0	1	0
	211	38	24

The statement may be considered as proven that vaccination has changed the age incidence of smallpox. *It is a rarity for a successfully vaccinated child under five years of age to die of smallpox.* It is even uncommon for a successfully vaccinated child under ten years to succumb to the disease, as will be seen from the following table compiled by the British Royal Vaccination Commission:

SMALLPOX IN CHILDREN OF THE AGE OF ONE TO TEN YEARS.

	Vaccinated.	Not vaccinated.
Attacks	570	1235
Deaths[1]	16	375
Fatality, per cent	2.8	30.3

The saving of infant life by vaccination should have reduced the general infant mortality in the postvaccination period.

The *opponents of vaccination* urge that the decline of mortality from smallpox at the beginning of the nineteenth century was not due to vaccination, but to the *discontinuance of inoculation.*

It is probable that inoculation did tend to increase the *prevalence* of smallpox, but there is no evidence to prove that it increased the *mortality.* As the Royal Commission remarks: "It must be borne in mind that inoculated smallpox was on the whole much less fatal than that naturally acquired. The class of inoculated persons may thus have contributed less to the fatal cases of smallpox than if they had been left to the chances of natural contagion."

While inoculation was introduced into England in 1721, it found but little favor until 1740. The Suttons popularized the practice in 1763, and between 1770 and 1780 it was widely employed. Inoculation was, therefore, only practised on a large scale in England in the second half of the eighteenth century, and particularly in the last twenty-five years of this period. The antivaccinationists claim that the increase of smallpox mortality in the eighteenth century over the seventeenth was due to the practice of inoculation. If this were true the mortality should

[1] Six of these deaths occurred in children in whom the success of the vaccination was doubtful.

have shown its increase particularly during the second half of the century. But the mortality was as great (if not greater) during the first quarter, when there was practically no inoculation, as during the last quarter of the century, when inoculation was greatly in vogue.

In *Sweden*, where inoculation was never practised to any extent, the fall in smallpox, after the introduction of vaccination, was as pronounced as in any country.

Again, it must be remembered that inoculation did not entirely cease in England upon the introduction of vaccination, but continued to be practised for a number of years, until it was declared illegal by act of Parliament in 1840.

It is evident from these considerations that the discontinuance of inoculation was to no appreciable extent the cause of the diminution of smallpox mortality at the beginning of the nineteenth century.

It has also been claimed by the opponents of vaccination that the decline in the prevalence of smallpox, dating from the beginning of the nineteenth century, was due to *improvement in sanitary conditions*.

It may be conceded that such improvements as better drainage and sewerage, freer ventilation, purer water supply, lessened crowding in dwellings, and the like would, by improving the average individual health, tend to lessen the fatality of all infectious diseases, not excluding smallpox. But such influences are totally inadequate to explain the striking and progressive decline in the prevalence and mortality from smallpox that followed the introduction of vaccination.

If sanitary improvements were responsible for the lessened mortality from smallpox, why did they not similarly influence the mortality from measles, scarlet fever and whooping cough, which are favored by the same conditions that aid the dissemination of smallpox? Smallpox and measles resemble each other in the sense that the spread of both diseases is not dependent upon any special sanitary defect. Unlike typhoid fever and cholera, their occurrence is influenced by personal infection rather than by any definite vices of sanitation. Measles and smallpox are the most contagious of all diseases; a momentary exposures of an unprotected person to the infection of smallpox or measles suffices for such individual to contract the disease. According to the Registrar General's Reports, during the same period in England that *smallpox* mortality has declined 72 per cent, the mortality from *measles* has fallen only 9 per cent. Furthermore, the death-rate from whooping cough has declined but a little more than 1 per cent, and the diminution in the mortality of scarlet fever has only become apparent within comparatively recent years. Again, the improvement in sanitation and mode of living has only caused a reduction of the general death-rate of the country of 9 per cent.

Another noteworthy fact must not be forgotten—namely, that the decline in the death-rate from smallpox has been entirely limited to persons below the age of fifteen years. It is evident, therefore, that the lives of an enormous number of children have been saved. Above fifteen years of age the smallpox mortality for obvious reasons has not

decreased. It is the height of absurdity to attempt to explain such an inequality in the decline of smallpox mortality on the grounds of improved sanitation. The percentage of mortality borne by children the subjects of measles, scarlet fever and whooping cough does not differ materially from what it was a century ago.

Smallpox in the Vaccinated and Unvaccinated.—If vaccination had no protective influence against smallpox it would be logical to conclude that there should be no material difference between the mortality of this disease in vaccinated and unvaccinated persons. But the experience of over one hundred and twenty-five years offers *absolutely conclusive proof that there is a most pronounced difference in smallpox mortality in these two classes.* There has never been an epidemic of

FIG. 27.—Two sisters suffering from smallpox. The one on the right, aged fourteen, was successfully vaccinated in infancy; she contracted a mild varioloid and recovered without any scarring. The other, unvaccinated, developed a severe smallpox, confluent on face and arms, finally recovering although considerably pitted.

smallpox in any country of the world in which the death-rate among the vaccinated has not been decidedly lower than that among the unvaccinated.

Epidemics of smallpox, like epidemics of all infectious diseases, vary greatly in malignancy. Diphtheria, scarlet fever, measles and in fact all of the transmissible diseases appear at times in virulent form accompanied by high mortality, and at other times in mild form with correspondingly lower death-rates.

These variations apply equally well to smallpox, and are produced by circumstances, the nature of which are poorly or not at all understood. When severe epidemics of smallpox prevail the mortality-rate is increased both among the vaccinated and unvaccinated. Variations

in the severity of the disease, however, need not in the least degree complicate the comparative study of the fatality in the vaccinated and unvaccinated.

FIG. 28.—Same patients as in Fig. 27, showing appearance after recovery.

DEATH-RATE OF SMALLPOX AMONG VACCINATED AND UNVACCINATED IN VARIOUS COUNTRIES.

Places and times of observation.	Total number of cases observed.	Death-rate per 100 cases.	
		Among the unvaccinated.	Among the vaccinated.
France, 1816–1841	16,397	16.125	1.00
Quebec, 1819–1820	?	27.00	1.67
Philadelphia, 1825	140	60.00	0
Canton Vaud, 1825–1829	5,838	24.00	2.17
Darkehmen, 1828–1829	134	18.80	0
Verona, 1828–1829	909	46.67	5.67
Milan, 1830–1851	10,240	38.33	7.67
Breslau, 1831–1833	220	53.80	2.11
Würtemberg, 1831–1835	1,442	27.33	7.10
Carniola, 1834–1835	442	16.25	4.40
Vienna Hospital, 1934	360	51.25	12.50
Carinthia, 1834–1835	1,626	14.50	0.50
Adriatic, 1835	1,002	15.20	2.40
Lower Austria, 1835	2,287	25.80	11.50
Bohemia, 1835–1855	15,640	29.80	5.17
Gallicia, 1836	1,059	23.50	5.14
Dalmatia, 1836	723	19.67	8.25
London Smallpox Hospital, 1836–1856	9,000	35.00	7.00
Vienna Hospital, 1837–1856	6,213	30.00	5.00
Kiel, 1852–1853	218	32.00	6.00
Würtemberg, no date	6,258	38.90	3.50
Malta, no date	7,570	21.07	4.20
Epidemiological Society returns, no date	4,624	19.70	2.90

The figures on p. 117 show that among thousands of cases of smallpox occurring in cities all over the world the *death-rate from smallpox has been from five to sixteen times greater among the unvaccinated than among the vaccinated.*

In a period covering twenty-one years from 1835 to 1855 in Prague official returns show that, whereas *one-third of all unvaccinated* cases of smallpox died, but *one-nineteenth of the vaccinated* cases succumbed to the disease.

The following figures of an epidemic of smallpox at Marseilles in 1828 indicate the marvellous fact that but 0.5 per cent of the vaccinated died of smallpox, whereas among the unvaccinated the death-rate was 25 per cent. The *fatality among the unvaccinated was therefore fifty times greater than among the vaccinated.*

Marseilles, 1828.	Number.	Cases of smallpox.	Deaths by smallpox.
Total number of persons at ages (0 to 30) which were almost exclusively susceptible .	40,000	6020	1024
1. Protected by previous smallpox . .	2,000	20	4
2. Protected by vaccination	30,000	2000	20
3. Unvaccinated	8,000	4000	1000

Chemnitz[1] **(Saxony).**—According to Dr. Flinzer, the population of Chemnitz at the time of the epidemic of 1870–1871 was 64,222; of this number, 53,891, or 84 per cent, were vaccinated and 5712, or 9 per cent, were unvaccinated; in addition, 4652, or 7.3 per cent, had previously had smallpox.

Of the vaccinated, 935 took the disease and 7, or 0.7 per cent, died; of the unvaccinated 2643 took the disease and 243, or 9.2 per cent, died. The mortality among the *unvaccinated was almost twelve times greater than among the vaccinated.*

The relative mortality from smallpox for the unvaccinated population was *three hundred and twenty-six times greater* than for the vaccinated.

The British Royal Commission on Vaccination presents the statistics of six epidemics in Dewsbury 1891–1892, Warrington, 1892–1893, Leicester 1892–1893, London 1892–1893, Gloucester 1892–1893 and Sheffield. A grand total of 11,065 attacks is collected; this number resulted in 1283 deaths, or 11.5 per cent, divided as follows:

	Vaccinated.	Unvaccinated.
Cases	8744	2321
Deaths	461	822
Per cent	5.2	35.4

The death-rate is, therefore, *seven times greater among the unvaccinated than among the vaccinated.*

If children under ten years of age are alone considered, the result is still more remarkable.

	Children under the age of ten years.	
	Vaccinated.	Unvaccinated.
Cases	589	1449
Deaths	16	523
Per cent	2.7	36.0

[1] Quoted by Immerman: Loc. cit.

If vaccination confers no protection against smallpox, how can this signal difference in the death-rates of the two classes be explained? Some influence must have been at work which caused the one class to suffer less fatality than the other.

Eliminating all children under one year of age (who might by reason of tender age fall easier prey to the disease), the Commission still found the most striking difference in the fatality. Among the vaccinated the death-rate was 2.8 per cent as compared with 30.3 per cent in the unvaccinated.

It is impossible to evade the conclusion that vaccination, being the only circumstance to differentiate the two classes, must have been the influence operating.

Evidence of Influence of Vaccination Against Attacks of Smallpox.—Thus far figures have been cited to prove that vaccination lessens the fatality of smallpox. It has been shown that the death-rate of smallpox among the vaccinated is decidedly lower than among the unvaccinated, and that the relative mortality of smallpox among a vaccinated population is strikingly less than among an unvaccinated one. It remains to present evidence of the influence of vaccination in the attack-rate of smallpox. The British Royal Commission on Vaccination gives the following census concerning the epidemic in Sheffield:

SHEFFIELD ATTACK-RATE.

	Vaccinated.	Unvaccinated.
Population	268,397	5715
Attacked by smallpox	4,151	552
Per cent	1.55	9.7
Children under 10 years	68,236	2259
Attacked by smallpox	353	228
Per cent	0.50	10.1
Persons 10 years and upward	196,905	3429
Attacked by smallpox	3,774	322
Per cent	1.90	9.4

It is seen from the above figures that the attack-rate among vaccinated children under the age of ten years was only 0.5 per cent, as compared with 10.1 per cent among the unvaccinated. Over the age of ten the attack-rate among the vaccinated was 1.9 per cent, and among the unvaccinated 9.4 per cent.

The following table, which presents the figures of five epidemics in England gives results which are remarkably uniform:

	Attack-rate under 10 years.		Attack-rate over 10 years.	
	Vaccinated.	Unvaccinated.	Vaccinated.	Unvaccinated.
Sheffield	7.9	67.6	28.3	53.6
Warrington	4.4	54.5	29.9	57.6
Dewsbury	10.2	50.8	27.7	53.4
Leicester	2.5	35.3	22.2	47.6
Gloucester	8.8	46.3	32.2	50.0

It is evident from the above comparisons that the lessened liability to attack among the vaccinated as compared with the unvaccinated is

much more conspicuous among children under ten years of age than in a more advanced period of life.

Attack-rate in Invaded Houses.—In Sheffield, of 18,020 vaccinated persons of all ages living in infected houses, 4151, or 23 per cent, were attacked. Of 736 unvaccinated persons under the same conditions, 552, or 75 per cent, were attacked. When children under ten years are alone considered the results are remarkable. Of 4493 vaccinated children in infected houses, 353, or 7.8 per cent were attacked; of 263 unvaccinated children, 228, or 86.9 per cent, were attacked. *Ten out of 11 of the vaccinated* children escaped, while but *1 out of 8 of the unvaccinated* children failed to take the disease.

Similar ratios were noted in the epidemics in Leicester, Dewsbury and Gloucester.

REVACCINATION STATISTICS.

It is a well-known fact that the protection conferred by vaccination against smallpox becomes impaired in the course of time and may, indeed, be lost entirely. The protection, however, may be restored by a second vaccination, and in the majority of individuals such revaccination will protect against smallpox for life.

It is, of course, understood that a person upon whom an unsuccessful revaccination has been performed is not revaccinated. Revaccination means a second attack of vaccinia and not merely the rubbing of virus into the skin. The failure of a secondary vaccination does not necessarily indicate an immunity against vaccinia and variola, but may be due to faulty virus or technique; or the subject may be for a time immune and later redevelop a susceptibility to both infections.

We have learned that vaccination lessens both the incidence and the mortality of smallpox. *Successfully revaccinated persons are attacked by smallpox much less frequently than those once vaccinated*, and the mortality-rate is further reduced. In proof of this proposition the following statistical evidence gathered by the British Royal Commission on Vaccination is presented.

During the epidemic of smallpox in *Sheffield* in 1887 there were in the town 64,431 revaccinated persons. Of this number, 17 were attacked by smallpox, with 1 death. (This man had been revaccinated eighteen years previously, in 1869.) The *attack-rate* of the revaccinated was, therefore, 0.04 per cent.

The attack-rate of vaccinated persons over the age of ten years, as enumerated in the census, was 1.9 per cent, and of the unvaccinated persons of the same age period 9.4 per cent.

In *Leicester*, during the epidemic of 1892 1893, in a group of 133 houses with 842 inmates, 141 persons were attacked; among 84 revaccinated inmates but 1 was attacked. In another group of 60 houses there were 392 inmates, of whom 179 were attacked; among 31 revaccinated persons 5 contracted the disease.

In the first group the attack-rate among the revaccinated was 1.1

per cent, as against 14.6 per cent, in the entire vaccinated class. In the second group of houses, which were evidently more intensely infected, the attack-rate among the revaccinated was 16.1 per cent, among the vaccinated 35.3 per cent and among the unvaccinated 59.6 per cent.

In *London* in 1892–1893 there were 108 attacks in revaccinated persons, of which 101 were mild and 7 severe. In this class there were 4 deaths, showing a mortality of 3.7 per cent. Among vaccinated persons over ten years of age the mortality was 4.2 per cent and among the unvaccinated at this age period 20.9 per cent.

In *Warrington* in 1892–1893 there were 64 revaccinated persons in the invaded houses; of these 8, or 12.5 per cent, were attacked. The percentage of vaccinated inmates attacked was 29.9 per cent and unvaccinated 56 per cent. There were 41 inmates who had previously had smallpox; of this number, 5, or 12.1 per cent, were attacked. There were no deaths among the revaccinated or among those suffering a second attack of smallpox.

The above evidence concerns comparatively recent epidemics. Revaccination was practised at an early date in some of the armies of the European countries, particularly among the *Würtemberg* troops (1833). Heim says that in five years there occurred among 14,384 revaccinated soldiers in Würtemberg, only *1 instance of varioloid*, and among 30,000 revaccinated persons in civil life only *2 cases*, although during this time smallpox had prevailed in 344 localities and had produced 1674 cases of smallpox among the not revaccinated and in part not vaccinated population of 363,298.

In the *Baden* army between 1840 and 1868, according to Kussmaul, there were performed 100,546 revaccinations, of which 40,040, or 39.8 per cent, were successful. During this period of thirty-nine years there occurred in the army 359 cases of smallpox. Of this number only 34 were in the successfully revaccinated, while 325 were in the non-vaccinated, or, at least, in the unsuccessfully revaccinated.

Value of Revaccination as Illustrated in the Comparative Smallpox Losses of the French and German Armies in 1870.—The entire German field army, which numbered over 1,000,000 soldiers, although exposed to a raging smallpox epidemic in France, lost by death from this disease *297 men;* the French army, on the other hand, suffered the enormous loss of *23,469 men* from smallpox. (It will presently be shown that the German troops were well vaccinated and the French soldiers poorly vaccinated.)

The mortality-rate from smallpox of the German soldiers in the field was 5.97 per cent. Of the stationary or immobile German troops, 3472 were attacked, of whom 162 died, giving a mortality-rate of 4.6 per cent. The aggregate number of German soldiers attacked, including those in the field and the stationary troops, was 8463, of whom 459, or 5.42 per cent, died.

The number of cases in the French army is not known, but the *death-rate was forty-nine times greater than in the German army.*

Moreover, the death-rate of smallpox in the German army compares very favorably with the death-rate of the civil population of Germany. In the entire army, stationary and in the field, there were 459 deaths from smallpox; in the Prussian kingdom in 1871 there were 59,839 deaths from the same disease. Still more striking is the comparison of the death-rate between the army and the inhabitants of Berlin. In this city of 826,341 population a much smaller number than that comprising the army, the deaths from smallpox were 5508.

It is known that the *Prussian army*[1] *was well vaccinated* up to the time of the war, when the vaccine supply became insufficient. Nearly all of the soldiers of the Germany army had been vaccinated in childhood and again upon entrance into the army, for that custom had been enforced for a number of years.

The French army, on the other hand, was poorly vaccinated. From 1832 to 1859 smallpox caused 39 per cent of all deaths in the French army. In 1857 an order was issued that all recruits be vaccinated without regard to the presence of previous scars, and the smallpox deaths during 1862–1872 fell to 19 per cent, exclusive of the year of the war. It is evident, however, that vaccination was only partially practised, for official record shows that in 1866, of 45,064 recruits, but 33,513 were vaccinated; in 1868, of 82,203 recruits, only 47,324 were vaccinated; in 1869, of 115,876 recruits, only 54,720 were vaccinated; in other words, in 1869, 61,156, or over one-half the recruits, were not vaccinated on entrance into the army. Furthermore, a large proportion of the vaccinations performed were without result; of first vaccinations 51 to 63 per cent failed, and on repetition 66 per cent failed.

That locality did not cause the discrepancy in the death-rate of the French and German soldiers is shown by the fact that the smallpox mortality among the French prisoners on German soil was 1963, while the entire German army on German soil lost but 162 men.

France greatly profited from this bitter lesson.

In the *thoroughly well-vaccinated French army in the recent World War not a death from smallpox occurred up to June, 1917.*

The remarkable results of vaccination and revaccination in the German army, particularly when compared with those in the French army and with the civil population of Germany during the Franco-Prussian War, led to the adoption by the German government of a law making vaccination and revaccination compulsory. This was passed, April 8, 1874, and went into effect on April 1, 1875.

Its essential provisions are as follows: Every child must be vaccinated before the expiration of the first year of its life, unless it has had smallpox or unless some physical disability exists; in the latter event the vaccination is undertaken within one year of the removal of the existing disability. Every pupil of a public or private educational institution must be vaccinated between the age of thirteen and

[1] Edwardes: Loc. cit.

fourteen years, unless there is medical proof that he has had an attack of smallpox within five years or has been successfully vaccinated within that time.

Parents, caretakers, guardians or heads of schools who fail to comply with the law are subject to fine or imprisonment. Vaccination must be performed only by physicians, and anyone vaccinating illegally is punished by a fine not exceeding 150 marks or imprisonment not exceeding fourteen days.

The Results of the German Compulsory Vaccination Law.—If there was in existence no other statistical evidence of the efficacy of vaccination and revaccination, the history of smallpox in Germany since 1875 would be all sufficient testimony.

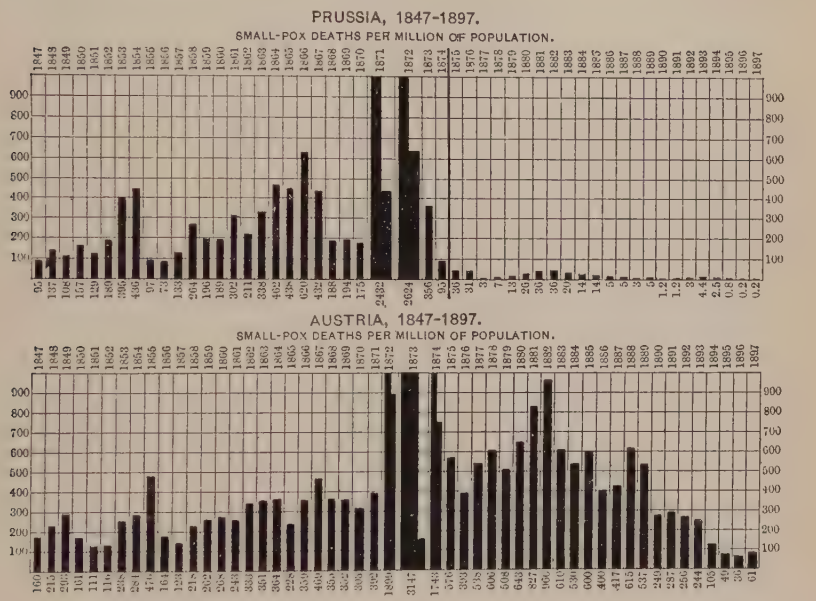

PRUSSIA, 1847-1897.
SMALL-POX DEATHS PER MILLION OF POPULATION.
AUSTRIA, 1847-1897.
SMALL-POX DEATHS PER MILLION OF POPULATION.

FIG. 29.—Tables showing the decline of smallpox in Germany after the enaction of compulsory vaccination in 1874; smallpox mortality is compared with that of Austria.

From 1816 to 1870 the annual mortality from smallpox in Prussia varied from 7.32 to 62 per 100,000 of population. This death-rate was small compared with the prevaccination periods.

During the disastrous pandemic of 1871–1872 the rate was 243.2 and and 262.67, respectively. *After the law of* 1875 went into effect the *annual mortality in Prussia fell* so that between 1875 and 1886 the average yearly mortality per 100,000 of population was 1.91, the maximum reaching 3.6 (in 1877).

On the other hand, in *Austria,* where the lax vaccination and revaccination requirements remained unchanged, the *mortality-rate* from smallpox during about the same period (1875 to 1884) *increased,* varying between 39.28 (1876) and 94.79 in 1882 (Fig. 29).

The results of the German vaccination law in the principal states of the Empire are given in the following table:

THE RESULTS OF THE GERMAN VACCINATION LAW, 1874.

Smallpox Deaths per 1,000,000 *Living.*

1. *Before the Law of* 1874.

Year.	Prussia.	Bavaria.	Würtemberg.	German Empire.	Contrast Austria.
1866	620.0	120.0	133.0	..[1]	368
1867	432.0	250.0	63.0	..	484
1868	188.0	190.0	19.0	..	370
1869	194.0	101.0	74.0	..	374
1870	175.0	75.0	293.0	..	293
1871	2432.0	1045.0	1130.0	..	383
1872	2624.0	611.0	637.0	..	1866
1873	356.0	176.0	30.0	..	3094
1874	95.0	47.0	3.0	..	1725

2. *Since* 1874.

1875	36.0	17.0	3.0	..	576
1876	31.0	13.0	1.0	..	406
1877	3.4	17.0	2.0	..	555
1878	7.1	13.0	0	..	631
1879	12.6	5.0	0	..	534
1880	26.0	12.0	5.6	..	674
1881	36.2	15.0	3.6	..	807
1882	36.4	12.0	6.6	..	947
1883	19.6	6.0	35.2	..	596
1884	14.4	1.0	11.6	..	530
1885	14.0	3.0	.0	..	600
1886	4.9	1.0	1.0	4.2	400
1887	5.0	1.8	0	3.5	417
1888	2.9	3.8	0.5	2.3	615
1889	5.4	5.2	0	4.1	537
1890	1.2	1.5	0	1.2	249
1891	1.2	1.2	0	1.0	287
1892	3.0	0.5	0	2.1	256
1893	4.4	0.7	1.0	3.1	244
1894	2.5	0.3	0	1.7	105
1895	0.8	0.2	0	0.5	49
1896	0.2	0.2	0	0.2	36
1897	0.2	0	0	0.1	61
1898	0.4	0.3	0	0.3	
1899	..	..	..	0.5	

[1] No statistics.

The remarkable results of compulsory vaccination and revaccination in Germany are perhaps the more striking when the mortality-rate of smallpox in German cities is compared with cities of other countries. After compulsory revaccination in 1875 the average annual death-rate from variola from 1875 to 1886 in the following cities was as follows:

DEATH-RATE FROM SMALLPOX PER 100,000 OF POPULATION.

German Cities.	Persons.	*Other Cities.*	Persons.
Berlin	1.16	Paris	26.24
Hamburg	0.74	St. Petersburg	35.82
Breslau	1.11	Vienna	64.90
Dresden	1.03	Prague	147.90

There is but one explanation for the marvelously low death-rate in the German cities as compared with other continental centers; that explanation is *careful and uniform vaccination and revaccination.*

A comparison of total *smallpox attacks* in the German, French and Austrian armies after 1875 is equally instructive:

	Men.
German army (1875–1887)	148
French army (1875–1881)	5,605
Austrian army (1875–1886)	10,238

In the German army, despite greater numbers and a longer period of time, the smallpox attacks were enormously less than in the French and Austrian armies.

The following figures indicate the prevalence of smallpox on the German frontier as compared with the interior.

The mortality from smallpox in Germany from 1886 to 1889 was:

	At the frontier, cases.	In the interior, cases.
1886	110	45
1887	119	49
1888	94	16
1889	188	12

Furthermore, for a *period of thirteen years* in a population comprising two-fifths of the total inhabitants of Germany, there were *only 5 instances of death from smallpox in successfully revaccinated persons.*

Germany has taught the world how to utilize Jenner's great discovery so as to exterminate smallpox as an epidemic disease.

The Incidence of Smallpox in Germany as Compared with England.—Since 1875 Germany has had a compulsory vaccination and revaccination law well enforced. In England, owing to anti-vaccination, agitation, the governmental vaccination requirements have gradually been weakened so that there is now a conscience clause which permits the father to have his children exempted from vaccination. Geographically England is in a far more favorable position than Germany inasmuch as she possesses an insular isolation whereas Germany is bordered by Eastern states in which smallpox is always extensively prevalent, and infection is being frequently introduced into Germany. Despite this fact, the smallpox history of Germany shows an infinitely better record than that of England and Wales. Except for the years 1917, 1919, and 1920, for reasons elsewhere stated, Germany has had a marvellous record of freedom from epidemic smallpox. Moreover Germany's population was in the neighborhood of 70,000,000 as compared with about 40,000,000 for England and Wales. The below appended tables give evidence of the greater incidence of smallpox in England.

SMALLPOX CASES AND DEATHS IN GERMANY FROM 1900 TO 1926.

Year.	Cases.	Deaths.	Deaths in 1,000,000 of population.
1900	392	49	0.90
1901	375	56	1.00
1902	114	15	0.30
1903	172	20	0.30
1904	189	25	0.40
1905	212	30	0.50
1906	256	47	0.80
1907	345	63	1.00
1908	434	65	1.00
1909	247	26	0.40
1910	236	34	0.50
1911	288	35	0.50
1912	340	35	0.50
1913	90	12	0.20
1914	138	18	0.30
1915	187	28	0.40
1916	685	93	1.30
1917	3028	456	7.50
1918	413	58	0.90
1919	5021	707	11.20
1920	2115	354	5.80
1921	689	100	1.60
1922	215	28	0.50
1923	17	2	0.03
1924	16	2	0.03
1925	24	9	0.14
1926	7	0	

Every country of Europe has some form of vaccination regulation varying from thrice required vaccination at birth, at school age and on entrance into the army, to enforcement as a prerequisite to school attendance. Of the great nations, Germany has the best carried out regulations. Germany has stamped out smallpox as an epidemic disease. Small epidemics occurred between 1916 and 1919 owing to contact with and invasion from poorly vaccinated Russia, Poland and Galicia and the general disorganization at the time of demobilization of the soldiers.

Germany has had less total smallpox in the last fifty years than the United States ordinarily has in one year. The German vaccination law requiring vaccination in the first year and revaccination at the age of twelve years went into effect in 1875. *In the fifty-nine years prior to 1875 the average yearly number of deaths from smallpox was 6663. In the forty-eight years, from 1875 to 1924, the average yearly mortality was 171. In other words, before the law went into effect almost thirty-nine times as many people died of smallpox as afterward.* A similar condition of affairs occurred in Sweden. In Germany, with a population of about 62,000,000 people, there died from smallpox in 1923 and 1924 combined only 4 persons, a truly remarkable record.

The German Vaccination Commission of 1884, referring to the influence of the compulsory vaccination law, says:

"Previously to 1871 smallpox mortality in Austria behaved much

like that of Prussia, through higher on the whole. The great epidemic of 1872–1874 was more fatal and lasted longer than in Prussia. During the next two years the mortality fell, as usual after epidemics. Here the influence of the epidemic in lowering the mortality ceases, and the latter rises at once to its old figure, viz: as before the epidemic, and even higher, and this rise was not merely temporary.

"The remarkable and persistent decline in Prussia since 1875 can only be due to the vaccination law of 1874, *because all other conditions remain the same in the two countries.* The only difference is that in Prussia the revaccination of all school children at the age of twelve years was made compulsory in 1874."

The Board of Health of Berlin has prepared tables comparing the number of deaths occurring between the years 1886 and 1889 in countries having compulsory vaccination, and those without such provision:

Population.		Smallpox deaths.				Average of deaths.	Average per 1,000,000 of population.
		1886.	1887.	1888.	1889.		
Sweden,[1]	4,746,465	1	5	9	2	4	1
Ireland,[1]	4,808,728	2	14	3	0	5	1
Scotland,[1]	4,013,029	24	17	0	6	12	3
Germany,[1]	47,923,735	197	168	112	200	169	3.5
England,[1]	28,247,151	275	505	1,026	23	458	16
Switzerland,	2,922,430	182	14	17	3	54	18.5
Belgium,	5,940,365	1,213	610	865	1,212	975	164
Russia,	92,822,470	16,938	25,884	[2]	[2]	21,411	231
Austria,	23,000,000	8,794	9,591	14,138	12,358	11,220	510
Italy,	29,717,982	[2]	16,249	18,110	13,416	15,925	536
Spain,	11,864,000	[2]	[2]	14,378	8,472	11,425	963

[1] Compulsory vaccination.
[2] No statistics.

But a glance is necessary to show the striking difference between the number of deaths in those countries having compulsory vaccination and those in which there is no such measure. The average deaths per 1,000,000 in the compulsory vaccination countries is *eighty times* less than in the others. Furthermore, England is the least vaccinated of the compulsory countries and her death-rate is the highest among these.

From 1901 to 1910 there were only 380 deaths from smallpox in Germany. During the same period there were 4286 deaths in England and Wales, with only about one-half of Germany's population. Germany is moreover much more exposed to importation of smallpox from Russia, Poland, Galicia and other contiguous countries.

In well-vaccinated *Germany* but *1 person a year in every 1,000,000 died of smallpox between 1893 and 1897.*

In *England and Wales,* where vaccination was generally but not universally practised, *20 persons per 1,000,000 died each year.*

In *Austria*, where the vaccination laws are poorly enforced, *99 persons per 1,000,000 died each year.*

It is, indeed, quite possible to know to what extent vaccination is practised in the various countries by noting the mortality from smallpox.

There is an inverse proportion between these factors. It is evident, therefore, that in Spain and in Russia (including Asiatic Russia) vaccination must be greatly neglected.

Vaccination and Smallpox in Recent Years.—It may be stated as a general proposition, subject to but few exceptions, that the extent of smallpox in any given country is in inverse proportion to the amount of vaccination carried out in the said country. In some of the tropical countries or those in the Orient much vaccination is inefficacious because of the inertness of the lymph due to high temperature. Japan, for instance, has had an extremely high percentage of failures in first vaccinations in children as compared with Germany. Below is appended a list of European countries giving the smallpox deaths in each year from 1919 to 1924.

SMALLPOX IN EUROPE, 1919 TO 1924.

	Actual number of cases.						
	1919.	1920.	1921.	1922.	1923.	1924.	Total.
Norway (towns)	0	0	1	0	0	0	1
Sweden	7	11	2	0	0	1	21
Denmark	0	0	7	0	0	25	32
Belgium	42	91	21	23	31	31	239
Austria	411	253	18	4	17	0	703
France	572	392	341	172	195	210	1,882
Germany	5,021	2,115	689	215	17	16	8,073
England	311	280	336	973	2,504	3,784	8,188
Czecho-Slovakia	11,209	4,527	1,542	70	36	9	17,395
Italy	34,365	2,042	688	215	17	16	37,343
Russia(without Ukraine)	169,545	121,587	68,503	40,839	29,133	18,596	448,203
Japan	4,055	3,167	889	679	1,922	1,702	12,414
United States	56,332	96,684	102,787	32,800	29,968	51,429	370,000
British India (deaths)	136,077	101,329	40,446	40,836	41,571	46,374	406,363

The Scandinavian countries head the list for low incidence of smallpox; they all have well-carried out vaccination regulations. France's position has been greatly improved. In 1902 France passed a triple obligatory vaccination act, which requires vaccination in infancy and revaccination at the ages of eleven and twenty-one years.

France had a fearful smallpox incidence in her army in the War of 1870. In the World War *not a single case of smallpox developed* from 1914 to June, 1917.

Germany, which presents the most convincing vaccination statistics over nearly a half century, had a relatively high incidence of smallpox in 1919–1920. This was due to the demobilization of troops, to the

weakening of the administrative authority in carrying out vaccination, to the Polish invasions in upper Schleswig and to the unrestricted traffic between smallpox-stricken South Poland and Galicia and Germany. It is a significant fact that almost one-half of Germany's smallpox cases in the past quarter of a century has been in foreigners.

In Russian Poland before the World War there were yearly about 10,000 cases of smallpox with about 3000 deaths. When German troops occupied Poland smallpox was widely prevalent. The German civil government immediately vaccinated 5,000,000 inhabitants. Smallpox fell off from month to month and finally disappeared.

SMALLPOX CASES AND DEATH IN ENGLAND AND WALES DURING THE PAST SIXTEEN YEARS.

Year.	Cases.	Deaths.	Deaths in each 100,000 of population.
1911	295	23	0.06
1912	123	9	0.02
1913	113	10	0.03
1914	64	4	0.01
1915	90	13	0.04
1916	149	18	0.05
1917	7	3	0.01
1918	63	2	0.01
1919	294	28	0.08
1920	263	30	0.08
1921	315	5	0.01
1922	973	27	0.08
1923	2,485	7	0.02
1924	3,765	13	
1925	5,365	9	
1926	10,179[1]	18[1]	

A comparison of smallpox in Germany and in England since 1890 is here set forth.

SMALLPOX DEATHS.

England and Wales.		*Germany.*	
Year.	Deaths.	Year.	Deaths.
1890	16	1890	58
1891	49	1891	49
1892	431	1892	108
1893	1457	1893	157
1894	820	1894	88
1895	223	1895	27
1896	541	1896	10
1897	25	1897	5
1898	253	1898	15
1899	174	1899	28
1900	85	1900	49
1901	356	1901	56
1902	2464	1902	15
1903	760	1903	20
1904	507	1904	25
1905	116	1905	30
1906	21	1906	47
1907	10	1907	63
1908	12	1908	65
1909	21	1909	26
1910	19	1910	34

[1] Provisional low mortality due to mild type of smallpox prevailing.

Smallpox in the United States.—Owing to the sovereignty of the states vaccination legislation in the United States varies in the different states of the Union. Vaccination as a prerequisite to school attendance was first enacted in Massachusetts about 1855. Only fourteen states have this statute upon their books. Six states have no vaccination laws.[1]

Utah has an antivaccination law and compulsory vaccination is forbidden in Louisiana, except in the case of school children; in South Carolina, where quarantine may, however, be enforced on those refusing vaccination; in Minnesota, in the case of school children; in South Dakota.

In California, where a large number of antimedical cultists reside, opponents of vaccination have succeeded in developing a school population 80 per cent unprotected against smallpox.[2] This benighted state of public opinion has had its logical effect on the incidence of smallpox. Below is contrasted the number of cases of variola in California, New York and Massachusetts from 1915 to 1924:

	1919.	1920.	1921.	1922.	1923.	1924.
California	2002	4486	5581	2129	2028	9425
New York	191	307	631	255	391	491
Massachusetts	40	29	37	2	6	12

During this period California had the undesirable record of having had 25,651 cases of smallpox. New York, with hundreds of thousands of persons entering its port from every part of the world, had 2266 cases, and Massachusetts with a larger population than California, but with well-carried out school vaccination, had 126 cases.

Figures like these, and they can be duplicated in various parts of the world, are most eloquent.

Indifferent or unintelligent masses prompted by the ignorant pratings of faddists have placed the United States in the honor group with India and Russia. The United States has the unenviable distinction of ranking third among the civilized nations in the number of cases of smallpox.

Below is appended a record of which every moron in this country should feel proud:

SMALLPOX IN THE UNITED STATES, 1919–1924.

	Cases.
1919	56,332
1920	96,684
1921	102,787
1922	32,800
1923	29,968
1924	51,429

[1] An excellent résumé of the state regulations on vaccination is found in a small well-written book by Bernhard J. Stern, entitled Should We Be Vaccinated (Harper Brothers, 1927).

[2] Foce, J. N.: Am. Jour. Pub. Health, 1921, vol. 2.

During this period the United States had 370,000 cases of smallpox, or five times as many as Norway, Sweden, Denmark, Belgium, Austria, France, Germany, England, Czecho-Slovakia and Italy combined.

Fearful Smallpox Mortality in India.—The enormous loss of life from smallpox which still takes place at the present day may be appreciated from the appended number of deaths from this disease in British India:

1912	89,357
1913	98,156
1914	76,590
1915	83,282
1916	60,642
1917	62,277
1918	93,076
1919	136,077
1920	101,329
1921	40,446
1922	40,836
1923	41,571
1924	46,374
	970,013

It will be seen from the above that within a period of thirteen years smallpox cost almost 1,000,000 lives. To estimate the number of cases one would have to multiply this number by 4 or 5.

Immunity of Physicians and Nurses in Smallpox Hospitals.—If it can be demonstrated that physicians and nurses in smallpox hospitals are protected by vaccination, this must be regarded as a crucial test. For if these persons, living in the same atmosphere with scores or hundreds of smallpox patients, breathing in their very exhalations, are enabled to escape the infection, it certainly should be possible for others much less exposed to acquire similar immunity.

Experience shows that *physicians, nurses and others, if recently successfully vaccinated, may live in smallpox hospitals with perfect safety.* The immunity of employees (when properly revaccinated) is a uniform experience in practically all smallpox hospitals.

In the hospitals of London, from 1876–1879, there were admitted 11,412 smallpox patients who had been vaccinated in infancy, but not a single case was known to have occurred in a person who had been successfully revaccinated. It was the rule to revaccinate all nurses and employees before entering the hospital, and the number thus employed amounted to about 1000; of these only some half-dozen took smallpox, and they for some cause or other had escape revaccination.

Dr. Marson,[1] physician to the Smallpox Hospital of London for many years, giving evidence in 1871, stated that *during the preceding thirty-five years no nurse or servant at the hospital had been attacked with smallpox.*

[1] Edwardes, E. J.: The Practitioner, May, 1896.

Dr. T. F. Ricketts,[1] the medical superintendent of the Smallpox Hospital Ships on the Thames, shows that *out of 1201 persons* in attendance on board the smallpox ships since 1884 only *6 contracted the disease*, and all recovered. None of these persons had been successfully revaccinated before going on duty.

At the Southampton Fever Hospital all persons employed during the smallpox epidemic of 1893 were revaccinated before going on duty, and, although freely exposed to the disease, not a single individual contracted smallpox.[2]

According to Dr. Hill, of Birmingham, during the epidemic in 1893 over 100 persons were employed at the City Smallpox Hospital, all of whom had been recently revaccinated; *not one of them contracted smallpox.*

In the Philadelphia Hospital for Contagious Diseases, during a period of thirty-four years, in which time over 9000 cases of smallpox were treated, *we have not had a physician, nurse or attendant who had been successfully vaccinated or revaccinated prior to going on duty, contracted the disease.*

Indeed, during all of these years and among hundreds of persons in attendance on the sick, only 2 or 3 fell ill with mild attacks of varioloid, and these would have been avoided had not the exigencies of the occasion demanded that the attendants be immediately assigned to duty, without waiting for the vaccination to work out its immunity.

Physicians, nurses and others have no such immunity against other infectious diseases as against smallpox. According to Ernest Hart,[3] in 1893, of 2484 persons employed in the nine Metropolitan Fever Hospitals of London, 130 became infected and 2 died; 4 assistant medical officers, 10 nurses, 43 assistant nurses and 16 maid-servants were attacked with scarlet fever. Two assistant medical officers, 6 nurses and 15 assistant nurses contracted diphtheria.

The deaths from smallpox of *medical men* (who are particularly well vaccinated) were but *13 per 1,000,000* as against *73 per 1,000,000 of the general population* in England. In scarlet fever, on the other hand, against which physicians have no special protection, the figures are reversed; *59 medical men per 1,000,000 die of scarlet fever* as against *16* per *1,000,000* of the *general population.*

Experience of the Municipal Hospital of Philadelphia During the Epidemic of 1901–1904.—During this period over 3500 cases of smallpox were received at the hospital. No person who had been recently successfully vaccinated was admitted to the hospital with smallpox. Since the outbreak of the disease in the city it has been estimated that about 500,000 persons were vaccinated—about one-third of the population. If vaccination confers no protection against smallpox it is reasonable to suppose that some of these persons would have con-

[1] Report of the Metropolitan Asylums Board for 1892.
[2] Hart: Loc. cit.
[3] Hart, E.: Allbutt's System of Medicine.

tracted the disease and been brought to the hospital. (About 80 per cent of all the cases in the city were sent to the hospital.) But no such patient could be found among over 3500 admissions.

The experience of the Philadelphia and Chicago smallpox hospitals, which hundreds of medical students were permitted to visit in order to receive instruction at the bedside, is most impressive. Dr. Heman Spalding, Chief of the Bureau of Medical Inspection of the Department of Health of Chicago, stated before the Pennsylvania Vaccination

FIG. 30.—Two children in the Philadelphia Hospital for Contagious Diseases, one unvaccinated and the other vaccinated on the day of admission; the crust is still seen upon the leg. This child remained in the hospital with its mother (who was suffering from smallpox) for three weeks and was discharged perfectly well. The unvaccinated child admitted with smallpox died.

Commission, that he had since 1899 taken thousands of students from the various medical colleges of Chicago through the wards of the smallpox hospitals; the students were exposed for an hour or more to patients in all stages of the disease. The students were thoroughly vaccinated before being permitted to visit the hospital. Of the thousands of students receiving maximum exposure in smallpox wards not one contracted smallpox.

From 1901 to 1904, during an epidemic of smallpox in Philadelphia, about 700 medical students from the various colleges of medicine were

taken in small classes through the smallpox wards of the Philadelphia Hospital for Contagious Diseases for instruction. The students remained for one to two hours in an intensely infected atmosphere, exposed to the severest types of smallpox. At one time over 300 cases of smallpox were in the various wards.

The deans of the various medical colleges were previously instructed to see that the students were properly vaccinated. On reaching the hospital the students were in the habit of showing their vaccination marks, to obtain an opinion as to whether they were adequately protected. It happened that there was one student (who was later said

FIG. 31.—Three members of a family brought to the Philadelphia Hospital for Contagious Diseases with the mother who was suffering from smallpox. The child in the centre was unvaccinated; the other two had been vaccinated a year before because of the school vaccination requirements. These two children remained in the smallpox wards several weeks and left the hospital perfectly well.

to have been opposed to vaccination) who evaded vaccination. He contracted a severe attack of smallpox and was subsequently brought back to the hospital for treatment. All of the remaining students were perfectly protected. The unvaccinated medical student alone took the disease.

The experience of the Chicago and the Philadelphia smallpox hospitals just mentioned must convince one of the efficacy of vaccination. When one considers the extremely contagious character of smallpox, the almost universal susceptibility to it and the prolonged exposure of thousands of students to concentrated smallpox infection, it is impos-

sible to conceive of their escape without the operation of some common protective influence.

During the epidemic of 1901–1904 about 200 persons, including physicians, nurses, ward-maids, cooks, laundresses and the like were employed in the smallpox department, and *not one* contracted the disease.

These facts are not wondered at by those who are familiar with smallpox; they are anticipated. Evidence of this same nature has accumulated for nearly a half-century. Every epidemic adds fresh

FIG. 32.—Showing the protective influence of vaccination. Unvaccinated mother with smallpox, and vaccinated daughter who remained perfectly well.

data. The immunity of revaccinated nurses and physicians against smallpox constitutes testimony in favor of the efficacy of vaccination which is irrefutable.

In every epidemic of smallpox that has occurred in Philadelphia within the past thirty years instances have been observed of whole families being removed to the hospital because of an outbreak of the disease in these families. In such instances the unvaccinated children have suffered and often perished, while those who were vaccinated remained perfectly exempt, although living, eating and sleeping in the

infected atmosphere for several weeks. *But we have yet to see unvaccinated children escape the disease under similar conditions of exposure.* Furthermore, we have more than once seen a vaccinated infant take its daily supply of nourishment from the breast of its mother who was suffering from varioloid, and the infant continue as free from smallpox as if the disease were 100 miles away and the food derived from the most wholesome source. This is evidence of the prophylactic power of vaccination that does not appear in mortality reports nor in statistical records.

Vaccination Laws Throughout the World.—In practically all of the armies and navies of the civilized world vaccination and revaccination are compulsory.

Germany's relative immunity from epidemic smallpox since the enactment of the compulsory vaccination and revaccination law of 1875 has led other countries to follow in her footsteps.

Japan adopted in 1885 a compulsory vaccination and revaccination law.

Hungary passed in May, 1887, a law requiring vaccination in infancy and revaccination at the age of twelve years.

Italy in March, 1892, adopted a law requiring vaccination in infancy and revaccination at the age of ten to eleven years.

Roumania in 1894 began to put into effect a law requiring vaccination and revaccination.

France passed a law on February 15, 1902, requiring a thrice compulsory vaccination, at the ages of one, eleven and twenty-one years.

Sweden requires that children must be vaccinated "before the age of three years."

Norway has indirect compulsion, requiring the vaccination of all school children.

Denmark.—A royal decree of April 3, 1810, made attendance at school, permission to receive confirmation and to be married in church, dependent on proof of vaccination. It also decreed compulsory vaccination in time of smallpox epidemics. Children must be vaccinated before the age of seven years.

Belgium has indirect compulsion through vaccination of school children.

Holland. The vaccination law of December 4, 1892, provides for the infliction of a fine on the teacher and pupil if an unvaccinated child is permitted to enter school.

England.—The present law requires that every child shall be vaccinated before reaching the age of six months; the penalties of this law may, however, be avoided by a declaration of conscientious objection to vaccination.

By reference to the above facts, it is seen that during recent decades the tendency has been in Europe to increase the rigor of the vaccination requirements. In England the exemption granted to conscientious objectors is the only step in the opposite direction. To any unpreju-

diced student of the conditions in England it is evident that the maintenance of the exemption clause is the result of the existence of a powerful organized opposition to vaccination, which exerts a considerable influence in Parliament. We are prone to believe that the first great epidemic of smallpox in England will sweep away the "conscience clause."

A study of the prevalence of smallpox in the various European countries will show that the prevalence of smallpox bears an inverse proportion to the thoroughness with which vaccination is carried out in such countries; some countries have excellent vaccination laws and a poor or relatively poor administration of the same.

There can be no question that Germany leads all other countries in the systematic administration of her vaccination statutes. Is it a mere coincidence that Germany has had a lower smallpox mortality than any great country of the world?

EFFECT OF GENERAL SANITATION ON SMALLPOX.

It has been contended by the opponents of vaccination that the decline in the mortality from smallpox during the past century has been due to improved sanitation. Overcrowding and density of population are insanitary conditions which would naturally favor the spread of all contagious diseases, including smallpox. But overcrowding in tenement houses and density of population exist today in no less and, indeed, in probably greater degree than they did a century ago.

Rapidity of travel and intermingling and movement of population, which naturally facilitate the introduction of infection from one locality or country to another, are obviously more operative as factors in the spread of smallpox today than a half century or a century ago. A person may become infected with smallpox in the heart of Russia today and manifest the disease only after he has entered this country.

The Report of the British Royal Commission on Vaccination (signed by 11 of the 13 surviving members), speaking of the influence of sanitation, remarks (Par. 78):

"If we recognize that in the course of the eighteenth century the general mortality, the relative number of deaths from all causes went on decreasing, and attribute, as has been done, this decrease to improved sanitary conditions, no such like decrease of smallpox took place. Again, the places which were deemed the most salubrious appear to have been visited by epidemics of smallpox as severe as those which fell on unhealthy places. Thus the epidemic in Chester in 1774 was undoubtedly a severe one, and yet Haygarth writes: 'The healthiness of Chester, as shown by statisticians, must appear so very extraordinary as to be almost incredible.'

"Furthermore, 'no evidence is forthcoming to show that during the first quarter of the nineteenth century these improvements differen-

tiated that quarter from the last quarter, or half, of the preceding century in any way at all comparable to the extent of the differentiation in respect to smallpox.'

"If we compare with smallpox an analogous disease of an equally contagious character, such as measles, we find absolutely no decline in the mortality of that disease in the period under consideration; on the contrary, we note an increase." (See Report of Royal Commission, Par. 60.)

Measles and smallpox are the most contagious of all diseases; the infection is conveyed through the air and almost the entire human family is susceptible. During the period mentioned, therefore, there is no disease which could be more properly compared with smallpox as regards morbidity and mortality than measles.

It is to be observed that a decline in smallpox mortality was noted in Western Europe in countries where insanitary conditions continued to prevail.

The Report of the Royal Commission concludes upon this point as follows (Par. 55): "Upon the whole, then, we think that the marked decline of smallpox mortality in the first quarter of the nineteenth century affords substantial evidence in favor of the protective influence of vaccination."

It is most fallacious to consider the influence of general sanitation as applicable to all infectious diseases. Now that bacteriology and preventative medicine have enlarged our knowledge of the causes and means of prevention of various infectious diseases, we know that special diseases require specific means of prevention.

Cholera, typhoid fever and dysentery are largely due to infected water supply. The chief means of prevention is the securing of a pure source of water.

Malaria and yellow fever are due to the bite of certain species of infected mosquitoes. Protection against these diseases is secured by preventing the access of mosquitoes to patients suffering from malaria and yellow fever, and extermination of the mosquito as far as possible. It is through the employment of these measures that the building of the Panama Canal was made possible.

Typhus fever is conveyed, in large part, and perhaps exclusively, by the bite of the infected body louse. This explains the former frequency of this disease on dirty ships, in jails and crowded hospitals.

The plague is chiefly transmitted by the bite of fleas that live on infected rats and other rodents. The successful campaigns against the plague have been based on the extermination of these animals.

There remains a group of highly contagious diseases, including among other affections smallpox, chickenpox, whooping cough, measles and scarlet fever, in which the germ is carried through the air and inhaled. Smallpox and measles are the most readily transmissible of all diseases.

The Relatively Small Influence of General Sanitation on the Prevalence of Smallpox.—The study of the smallpox epidemic in Philadelphia from 1901 to 1904, inclusive, sheds an interesting light on the question of the influence of sanitation. During these years there were 5014 cases of smallpox in Philadelphia, with 890 deaths. From a chart of the infected houses in the city, prepared by the Bureau of Health, it is seen that there was an enormous preponderance of smallpox in the twenty-eighth and adjacent wards, in the immediate neighborhood of the smallpox hospital. There was likewise a great prevalence of smallpox along certain narrow streets through which the ambulance passed on its way to the hospital. The ward distribution of smallpox corroborates the view maintained by many distinguished experts, that a large smallpox hospital is a danger to the surrounding community, by reason of infection carried through the air, even over a considerable distance. For this reason, London, in 1885, established smallpox hospital ships.

It is quite possible that some infection may have been carried out from the Municipal Hospital by some careless employees, although there were strict regulations, etc., relating to employees of the hospital. Furthermore, smallpox developing in the families of employees was almost, if not quite, unknown.

During the years, 1901, 1902, 1903 the twenty-eighth ward and several of the neighboring wards, representing 26.71 per cent of the population of the city of Philadelphia, had 53.67 per cent of the smallpox cases. The twenty-eighth and adjacent wards consist mainly of small two- and three-story houses, many of them relatively new, in which single families reside. There are practically no tenement houses in these districts; generally speaking, the hygienic conditions are good.

Despite the latter fact, this section had an amount of smallpox entirely out of proportion to the population; this unusual incidence must be attributed to proximity to the Municipal Hospital.

The slum district comprised the first, second, third, fourth, fifth and sixth wards of the city, with a population of approximately 210,000, representing one-seventh of the population of the city.

This slum district is inhabited largely by a foreign population. It contains an enormous number of poorly constructed tenement houses in which numerous families live, often closely crowded together. It is not uncommon for six to ten people to be housed in a few rooms. It also represents the district in which there is the greatest poverty. Despite these unfavorable conditions, this district, representing 14 per cent of the entire population, merely had 5.5 per cent of the total smallpox mortality.

It cannot be urged that the smallpox mortality was small because the disease was so seldom introduced into this section of the city. The general fatality of smallpox throughout the city was about 18 per cent. As there were 50 deaths in the district referred to, there must have been in the neighborhood of 275 cases of smallpox in this section during four years.

The chief factor which gave this section so relatively low a smallpox incidence and mortality was the better vaccination of its people. The district contains tens of thousands of immigrants, who are vaccinated before landing in this country. Furthermore, there is little opposition to vaccination in the class of people who inhabit this section.

The facts strongly suggest that overcrowding, bad domestic hygiene, bad ventilation, poor food, poverty and like factors are infinitely less operative in favoring the spread of smallpox than the neglect of vaccination.

It should be further remarked that with respect to other contagious diseases, against which no prophylactic inoculation is employed, this district compares very unfavorably with other parts of the city. Scarlet fever and diphtheria occur in this district entirely out of proportion to the population.

Vaccination was not well carried out in those wards in which a high incidence of smallpox occurred. There were no admissions to the hospital of persons in whom a successful vaccination had been performed within a period of five years.

The experience of Philadelphia during the epidemic of 1901-1904 strongly supports the contention that general sanitary conditions play no important role in the control of smallpox.

Failure of Sanitary Measures Without Vaccination.—Cleveland, Ohio, had 1230 cases of smallpox in 1901. Dr. Martin Friedrich took office in July of that year. Owing to the inertness of much of the vaccine virus that was first employed and the very sore arms and infections caused by an impure virus later used, the Health Officer abandoned vaccination and determined to fight smallpox by sanitary measures alone. This campaign was begun toward the end of the epidemic when but 27 cases existed in the city. Smallpox disappeared for five months. The Health Officer then published an article in the *Cleveland Medical Journal*, of February, 1902, entitled, "How We Rid Cleveland of Smallpox." He stated that formaldehyde disinfection did it.

In March, 1902, smallpox again appeared in Cleveland, the infection being derived from Europe. Dr. Friedrich put into force notification, isolation, quarantine and disinfection. Disinfection was carried out in all suspicious quarters of the city on a scale seldom employed. Every general sanitary measure known to science was put into operation. Dr. Friedrich now admits that these "absolutely failed." Smallpox continued to spread until 1240 persons were attacked and 224 lost their lives. The doctor" tried to reintroduce vaccination, but the people were not ready to accept it; they had not suffered enough." "Vaccinating 200,000 in three months, we finally stopped smallpox in Cleveland."

Dr. Friedrich stated before the Pennsylvania State Vaccination Commission that after the epidemic of 1901 he had published an article in a medical journal endorsing the view that sanitary measures had

freed Cleveland of smallpox. Like an honest man, he admitted, "that was a mistake; I openly confessed that." The experience of the second epidemic convinced him that sanitary measures, without vaccination, could not control smallpox; much credit is due to Dr. Friedrich for his candid testimony under circumstances that could not be but embarrassing to him.

Opponents of vaccination have referred to the so-called Leicester "stamping-out system," as a means of preventing smallpox. The Leicester "stamping-out system" comprises neither more nor less than prompt notification, isolation, quarantine and disinfection, measures which are generally employed at the present time and which are recognized to be important aids in the suppression of smallpox.

A marked and progressive decline in vaccination had occurred in Leicester, England, for many years, so that in 1896, not more than 20 per cent of the children born were vaccinated.

While notification, isolation, quarantine and disinfection have kept an inland town of England relatively free from smallpox, this constitutes no guarantee that large cities more liable to the introduction of smallpox, by reason of the greater movement of population and the ingress of foreigners, would fare equally well. Cleveland relied upon this system in 1902, and the result was 1240 cases of smallpox and 224 deaths.

Furthermore, the "stamping-out system" failed to protect Leicester against outbreaks of smallpox in 1892 and again in 1902. In 1892, 357 cases of smallpox occurred in 193 households. In 1902 another outbreak of smallpox took place.

The epidemic in Leicester in 1892 was introduced by a tramp suffering from smallpox, the disease passing unrecognized. Herein lies the very kernel of the whole matter. Sanitary measures alone could only succeed in preventing and controlling smallpox, under a system whose perfection in every detail was guaranteed, a condition impossible to attain.

Failure to recognize the nature of the disease might, in an unvaccinated population, spell untold disaster, for scores of persons could readily be exposed to infection before isolation could be enforced. The secondary cases in turn would lead to further dissemination of the disease. This is the manner in which epidemics are produced.

Failure to call in a physician would prevent notification and isolation and thus permit dissemination of the infection. In Germany, in 1909, in no less than 21 cases of smallpox were no physicians called in. In an unvaccinated community this could readily have given rise to serious epidemics of smallpox.

Delay in calling a physician gives opportunity for many persons to be exposed to the smallpox patient. In Germany, in 1909, in 131 cases of smallpox the interim between the onset of the illness and the calling of a physician varied from one to sixty-two days, and averaged seven days.

Failure of the physician to diagnose smallpox is a common cause of extension of the disease. This may be due to the inexperience of the medical attendant, or may be the result of the inherent diagnostic difficulties of the case. Many diseases, particularly chickenpox, measles, syphilis and certain drug eruptions, may bear a close resemblance to smallpox when the eruption first makes its appearance. It is impossible to diagnose smallpox during the early initial fever. It is only recognizable when the eruption develops. Patients are commonly admitted to the wards of general hospitals with a fever which later proves to be that of smallpox. Among unvaccinated patients it is not difficult to surmise what would result.

The admission of a Pullman-car conductor to the wards of the Montreal General Hospital with a fever which proved to be smallpox, led in Montreal in 1885 to an epidemic which attacked 15,000 people and caused the loss of 3164 lives.

Further imperfection in the application of the system, such as incomplete isolation, escape from quarantine of contact persons, inadequacy of hospital accommodations, faulty disinfection of infected articles, etc., may lead to similar disaster.

A sanitary system for the prevention of smallpox without vaccination would require an eternal vigilance and a degree of perfection impossible to secure.

Furthermore, those living in a smallpox-stricken household would surely take the disease, without vaccinal protection. In addition, physicians, nurses, orderlies, servants, undertakers, etc., who are obliged to be exposed to infection, could not escape the disease without such protection. In Leicester, in 1892, among 6 nurses in the smallpox hospital who refused to be revaccinated, 5 contracted smallpox and 1 died.

The Antivaccination League of Great Britain distributed leaflets to third-class steamship passengers coming to America, counselling resistance to vaccination. The introduction of smallpox into the United States from Europe is ever a danger to this country. Our most serious epidemics arise from European sources. The rapidity of ocean travel makes it possible for a person to be infected in Russia, Italy or the Orient and to break out after arrival in the United States; during the latent period or stage of incubation it is, of course, impossible to detect the existence of the disease.

In June, 1912, a patient, convalescent from smallpox, embarked on the steamship "Haverford" at Liverpool. He was put off the boat at Queenstown. Some days after the arrival of the "Haverford" in Philadelphia smallpox developed in some of the passengers from this boat who had settled in different sections of Philadelphia, as well as in others who had gone to Wilkes-Barre, Scranton and Phillipsburg, N. J. Infection from this boat is said to have caused the serious outbreak of smallpox in Pittsburgh in which 114 persons were attacked, of whom 31 perished.

REASONS WHY OBLIGATORY VACCINATION IS DESIRABLE.

1. Because history proves that without obligatory vaccination it is impossible to secure a general vaccination of the community. In the absence of smallpox people cannot be depended upon voluntarily to seek vaccinal protection. Without statutory requirement, therefore, an unvaccinated population is bound to grow up.

The existence of a large unvaccinated population is a menace to the community, because the introduction of the spark of smallpox infection may lead to a general conflagration. To wait until smallpox is already in the community before carrying out vaccination is a deplorable policy for the following reasons:

(*a*) Because wholesale vaccinations must be carried out on thousands of people hastily and often without proper precautionary measures.

(*b*) Because exposed individuals may fail to take the vaccination and before a retrial is possible may contract smallpox.

(*c*) Because an unusually heavy demand may be made upon the supply of vaccine which may become exhausted; in the past, under such circumstances, the use of vaccine of questionable character has been resorted to.

(*d*) Because all of the attendant circumstances would, on the one hand, increase the risk of vaccination and, on the other, lessen the protective security attained by careful vaccination carried out gradually in the absence of smallpox.

2. The existence of a law upon the statute books requiring vaccination has a distinct educational influence.

The official endorsement of vaccination by the state is unquestionably accepted by the masses as evidence that it is a desirable health protective measure.

Per contra the expunging from the statute books of the provision requiring vaccination of school children would be regarded by the masses as a repudiation of vaccination. Such an act would unquestionably decrease the number of voluntary vaccinations, as a reflection would be cast upon the efficacy of the procedure.

Doubtless thousands of these children would not be vaccinated, were the law requiring vaccination as a condition precedent to school attendance not in existence.

But these non-vaccinations would in large part be the result of indifference or neglect rather than the result of opposition to the law.

The Argument—"Let Those Who Will, Protect Themselves."—Certain opponents of vaccination contend that vaccination should not be in any manner enforced by the state, but those who desire it should avail themselves of it. They furthermore argue that if vaccination protects, the vaccinated need have no concern as they cannot be menaced by the unvaccinated. If a method of fireproofing houses for a period of years were discovered, and if the frequency of fires made it desirable to pass a law requiring all houses to be fireproofed, the

opponents of such a measure might, with equal force, say "let those who desire such protection avail themselves of it; for ourselves, we are willing to run the risk." But their willingness to run the risk would in the natural course of events, increase the number of fires, would endanger houses in which the fireproofing was defective or had not been renewed, and would throw a great financial burden upon the community for the maintenance of fire houses, apparatus, etc.

So it is with vaccination: Neglect of vaccination by a large element of the population would, in the natural course of events, increase the prevalence of smallpox. Vaccination properly performed protects the individual against smallpox, but the protective influence may become weakened or even lost in the course of years and require renewal; the individual does not know when the safeguarding influence of vaccination has expired. Though a devout believer in vaccination, he might, through oversight, contract smallpox.

If smallpox were a prevalent disease, as it is in unvaccinated countries, it would be necessary to vaccinate infants as soon as they were born and to revaccinate oftener in order to make sure that the vaccinal immunity were still in continuance. If exposed to smallpox, children would have to be vaccinated, despite certain disabilities that would ordinarily lead to postponement of the operation. Just as those who are willing to run the risk would be encouraging the prevalence of fires increase the risk to others wherever and whenever a defect in the protection existed, so would the risk be increased for the vaccination conformists.

UNANIMITY OF OPINION AS TO THE VALUE OF VACCINATION.

There has probably never been in the history of mankind a great discovery the acceptance of which some men did not dispute. The great truth which Jenner gave to the world offers no exception to this general statement. There are dissenters who do not believe in vaccination, but they are chiefly to be found outside of the medical profession. *We know of no really eminent physician who is not convinced of the efficacy of vaccination;* those physicians who have had a large practical experience with smallpox are the most ardent advocates of vaccination, for they have had the best opportunity of noting the behavior of vaccinated individuals in the presence of smallpox. The few physicians who are found in the ranks of the antivaccinationists are usually men without large experience in smallpox; they argue with statistics (often unwittingly distorted) and not with facts derived from personal observation.

As a prophylactic remedy against smallpox vaccination was generally accepted by the medical profession at an early date.

In 1856 the Medical Officer of the London Board of Health, John Simon, sent circular letters to 542 prominent members of the medical profession in the United Kingdom and in some of the other European

countries, requesting their opinions as to the value of vaccination. Five hundred and thirty-nine replies were received and there was *absolute unanimity* as to the efficacy of vaccination as a protective measure against smallpox.

The most distinguished medical bodies in every country have time and time again affirmed their confidence in the protective influence of vaccination, and the most enlightened nations of the earth have officially recognized its value and have encouraged its practice.

Thomas Jefferson's appreciation of the value of Jenner's discovery may be judged from the following letter addressed to the discoverer of vaccination.

MONTICELLO, VIRGINIA, MAY 14, 1806.

SIR: I have received a copy of the evidence at large, respecting the discovery of the vaccine inoculation, which you have pleased to send me, and for which I return you many thanks. Having been among the early converts of this part of the globe to its efficacy, I took an early part in recommending it to my countrymen. I avail myself of this occasion to render you my portion of the tribute and gratitude due to you from the whole human family. Medicine has never before produced any single improvement of such utility. Harvey's discovery of the circulation of the blood was a beautiful addition to our knowledge of the ancient economy; but on a review of the practice of medicine before and since that epoch, I do not see any great amelioration which has been derived from that discovery. You have erased from the calendar of human afflictions one of its greatest. Yours is the comfortable reflection that mankind can never forget that you have lived; *future nations will know by history only that the loathsome smallpox has existed*, and by you has been extirpated. Accept the most fervent wishes for your health and happiness, and assurance of the greatest respect and consideration.

TH. JEFFERSON.

Thomas Jefferson's prophecy that "future nations will know by history only that the loathsome smallpox has existed" fails of fulfilment only because vaccination and revaccination are not universally adopted.

OPPOSITION TO VACCINATION.

It is a remarkable fact that despite one hundred and twenty-five years of incontrovertible testimony of the value of vaccination, there should still exist an organized antivaccination movement. To be sure the active opponents of vaccination comprise but a small percentage of the people, but their influence is none the less noxious. Their propaganda have consigned many thousands of smallpox victims to an untimely grave. Curiously enough the opposition to vaccination is most acute in the very country whence this great discovery sprang. Dr. James Gregory, the famous English smallpox physician of the middle of the nineteenth century, wrote, "England is a free country and the freedom which every free-born Englishman chiefly values is the freedom of doing what is foolish and wrong and going to the devil in his own way."

Opposition to vaccination on the part of different individuals has been due to various causes. Most antivaccinationists are zealous and sincere, but many in the early days and since have entered the arena for self-interest or to gain notoriety. Certain newspaper editors and

nature healers find it easier to obtain an audience by attacking vaccination than by the exercise of their mediocre talents in other directions.

It must not be forgotten however that some great men in England have opposed vaccination. John Bright was opposed to the compulsory feature of vaccination as was likewise Herbert Spencer. This was in accord with the latter's aversion to state interference. Alfred Russel Wallace was bitterly opposed to vaccination and believed that liberty was a more important matter than science. One finds other illustrious men, for instance, Bernard Shaw, ignorantly prating about the efficacy or rather the inefficacy of vaccination. In the preface to *The Doctor's Dilemma*, Shaw has the temerity to say: "Such monstrosities as vaccination are, as we have seen, founded not on science, but on half crowns. If the Vaccination Acts . . . were strengthened by compelling every parent to have his child vaccinated by a public officer, whose salary was completely independent of the number of vaccinations performed by him . . . vaccination would be dead in two years, as the vaccinator would not only not gain by it, but would lose credit through the depressing effects on vital statistics of his district of the illness and death it causes, whilst it would take from him all the credit of that freedom from smallpox which is the result of good sanitary administration and vigilant prevention of infection."

This profound ignorance of the subject on the part of one of the best dramatists of the day is incredible. If he meant these statements as entertaining irony then he trifles with human life. If he meant them seriously one must gasp at his self-sufficient audacity. Shaw is a brilliant philosophic satirist but a lamentably bad and, moreover a dangerous, sanitarian. His words are perhaps best to be interpreted as a manifestation of his rebellious spirit against all existing institutions.

When men, however otherwise great attempt to pass judgment upon scientific matters beyond the frontier of their experience they are prone to commit egregious blunders. In a matter of this character we must be guided by sanitarians and by medical scientists with large experience.

Antivaccinists are made up of laymen with restricted technical knowledge and a sprinkling of physicians who have some mental quirk which unfits them for a judicial interpretation of facts. Every scientific commission throughout the world that has ever investigated the efficacy of vaccination has affirmed its great value.

There is but one rational argument for opposition to vaccination, namely, that its practice is not entirely devoid of danger. But the danger is so slight in any individual instance that it is almost a negligible quantity. No human act is completely unattended with risk. When the extremely rare instances of death following vaccination are compared with the frightful slaughter of thousands by smallpox before the days of vaccination, and even at the present day in countries where vaccination is neglected, the benefits of Jenner's great discovery may be appreciated.

CHAPTER III.

THE VARIOLOUS DISEASES OF LOWER ANIMALS.

A NUMBER of domesticated animals appear to be susceptible to pock diseases which are more or less closely allied to human smallpox. These affections are, by reason of difference in behavior, divisible into two natural groups. The diseases comprised in the first group are communicable through the atmosphere; they are accompanied by a generalized eruption, and may be regarded as death-dealing pestilences; in this class are to be included human variola and sheeppox. In the second group the diseases are only capable of transmission by inoculation (accidental or intentional); the eruption is usually limited to the sites of inoculation, and death rarely takes place. In the second group belong cowpox, horsepox, apepox and other domestic animal pock diseases presently to be described.

Dr. Baron[1] says: "It seems certain that there are, at least, four animals, namely, the horse, the cow, the sheep and the goat, which are affected with a disorder communicable to man, and capable of securing him from what appears to be a malignant form of the same disease. It is, moreover, proved that other animals may take the vaccine disease by inoculation, and that matter taken from pustules so produced affords the genuine cowpox in man. The animals on which these experiments have been tried are the dog, the goat, the she-ass and the sheep. The fact as regards the dog was ascertained by Dr. Jenner."

Smallpox of Sheep.—*Sheeppox, variola ovina,* or *clavelée,* is an acute contagious and epizoötic disease characterized by symptoms closely simulating the manifestations of variola in the human subject.

Variola ovina is supposed to have arisen in Asia, and, like smallpox, to have extended thence to the continent of Europe. Various countries have from time to time experienced devastating epidemics which have greatly interfered with the sheep-growing industry.

Human Ovination.—Sacco inoculated about 300 children with the virus of sheeppox and claimed that the ovination protected them against smallpox. He states: "I subsequently determined to inoculate 2 children with ovine lymph on one arm and vaccine on the other; the vesicles were so similar in appearance that had I not marked the arms I should not have been able to distinguish the one vesicle from the other. A few days after the desiccation of the vesicles the children

[1] Life of Jenner, p. 243.

were inoculated with the virus of human smallpox, but no consequences, either local or general, resulted therefrom."

We believe that while the smallpox of sheep and that of man resemble each other clinically, and are doubtless closely related to one another, the two diseases are not identical. It would appear that sheeppox may at times be inoculated into the human subject, but there is no reason to believe in the intercommunicability of human and ovine variola by ordinary infection. No one has ever observed the smallpox of sheep give rise to smallpox in man, nor has the reverse route of infection ever been recorded.

Goatpox.—The existence of a primary goatpox is doubted by most authors, the view being held that this animal, which is zoölogically closely related to the sheep, contracts the disease from the sheeppox. The goatpox is accompanied by high fever and a generalized eruption. The disease is extremely rare.

That the goatpox is similar in its nature to cowpox appears probable from information contained in a letter written by Professor Heydeck to Dr. Dunning, and quoted by Baron. The letter reads: "The King ordered in September that all the children in the Foundling House should be inoculated with the goatpock, which did its effects."

Variola Equina, Horsepox, Grease or Eaux aux Jambes.—The various appelations here mentioned have been applied to a pock disease in the horse which bears a close relationship to vaccinia and variola. The term *grease*, Jenner tells us, was employed by farriers to designate this disease upon the heels of horses. It is regretted by some writers that Jenner used this term instead of variola equina, for the employment of this name has given rise to some confusion. Lupton,[1] in 1800, pointed out that the true analogy of cowpox in the horse was not the *grease* nor any form of *grease*, but a disease regarded by the neighboring farmers as widely different from it, and called by them "scratchy heel."

Loy, in 1801, distinguished two forms of grease, the acute and the chronic, the former of which alone was capable of imparting the disease to the bovine or human species.

Jenner briefly refers to grease in the following words: "The skin of a horse is subject to an eruptive disease of a vesicular character, which vesicle contains a limpid fluid, showing itself most commonly in the heels. The legs first become edematous, and then fissures are observed. The skin contiguous to these fissures, when actually examined is seen studded with small vesicles surrounded by an areola. These vesicles contain the specific fluid."

It will be seen from the above description that equine and bovine variola closely resemble each other. The disease in the horse distinguishes itself from that in the cow principally by the locality of the eruption—usually the heels and the naso-labial mucous membrane, the occasional tendency to generalization of the eruption and by attacking the male as well as the female.

[1] Med. and Phys. Jour., November, 1800, vol. 4.

The Relation of the Equine Disease to Cowpox.—Great interest attaches to this subject inasmuch as Jenner regarded *grease* as the progenitor of cowpox. Jenner informs us that in dairy counties in England it was frequently the custom for farm hands to dress the sores on horses and subsequently, without due attention to cleanliness, to milk the cows. In this manner infectious matter was carried to the teats of cows, producing the cowpox. From this source other cows and many of the dairy hands became infected.

Numerous experiments have proven the correctness of Jenner's assertion that cowpox results from inoculation with matter from the grease.

The belief entertained by Jenner, that the grease was the *invariable* source of natural cowpox, is not concurred in by most observers. There are many modern writers who are of the opinion that horsepox is nothing more than a variola or vaccinia accidentally derived from the human or bovine species. That the latter theory is correct is rendered probable in view of the fact that both cowpox and human variola may be transplanted to the horse with the production of horsepox.

Chauveau injected vaccine lymph beneath the skin and into the bloodvessels and lymphatics of colts, and produced a generalized eruption of horsepox.

Copeman remarks that in all probability Jenner was mistaken in his assumption that "grease," in the sense of horsepox, was a necessary antecedent to cowpox; but at the same time there can be little doubt that the two diseases are very closely allied, if, indeed, they be not identical."

We may assume that the two diseases have a common ancestry, without unavailingly attempting to adduce proof as to the priority of either. There is equal reason to believe that the hands of the groom may carry the infection from the cow to the horse as well as from the horse to the cow.

Human Equination.—Horsepox has been successfully inoculated into the human subject, with the production of vesicles similar to those observed in cowpox, and with the effect of conferring immunity against smallpox.

The Italian investigator, Sacco, in a letter written to Jenner in 1803, describes similar experiments: "A coachman came to the hospital for an eruption which he had on his hands. It was immediately recognized that he had contracted horsepox in caring for and dressing horses. I made nine inoculations (from the sores) on as many children. Three of these contracted an eruption exactly like that of vaccinia. I made other inoculations with the material from these children, and it has already been reproduced in four generations, with the same effect as the vaccine disease. I inoculated several of these individuals with smallpox, but without any effect. I also finally obtained, with the virus of grease inoculated into six other children, two lesions exactly like vaccine lesions."

Martin, of Boston, observed a case of casual horsepox in 1881, and obtained typical vaccine vesicles therefrom.

A number of other competent observers have confirmed the above experiments; so that it may be accepted that human beings can be equinated with virus taken from the horse, and that such inoculations protect against smallpox.

Retro-equination has been successfully essayed in horses with bovine or human virus of equine origin.

Natural Vaccinia, or Cowpox in the Cow.—Cowpox of spontaneous development is occasionally discovered in members of the bovine species. The disease in such cases is designated natural cowpox in contradistinction to the affection inoculated by design. Natural cowpox is an uncommon disease; indeed, it is so rare that to each case attaches an historical interest. From each cow with spontaneous cowpox a special strain of lymph is cultivated and perpetuated, so that these first sources are most highly prized. The disease is most apt to be observed in spring and early summer, when cattle yield the most milk; while any member of the bovine family (even the bull) may be attacked, it is particularly the milch cow in which the disease is found. The eruption is never generalized, but is circumscribed to the udders or their base. The location of the lesions constitutes strong evidence that the hands of the milker are the most important factor in the transmission of the disease. When the disease once appears in the herd it spreads with considerable rapidity from one cow to another.

Cowpox, both the natural and inoculated form, confers a permanent immunity against a second attack. No authentic case has been reported in which a cow has twice suffered from the disease.

Casual or Accidental Cowpox in Man.—It was from observation of cases of casual cowpox in dairy attendants that Jenner first conceived the theory of vaccination. These infections result from the contact of fluid from the lesions on the cow's teats with abrasions upon the hands of the milkers; one, two or more lesions are produced, according to the number of excoriations present. Upon areas of reddened skin there soon spring up vesicles or blebs, which are of a bluish color, rounded, flat and depressed in the center. These contain a lymph fluid which later becomes purulent. The surrounding skin becomes reddened and tumefied, owing to the development of an erysipelatoid areola about each lesion. The neighboring lymphatic glands become swollen and painful, and the patient becomes feverish. In severe cases the illness may be sufficiently pronounced to enforce confinement to bed for a few days. In a few days, however, there is an abatement of the local inflammatory disturbance and of the constitutional symptoms, and the pustules either become encrusted or form ulcers which gradually heal by granulation. In casual cowpox the local and constitutional symptoms are more severe than when the disease is intentionally inoculated, probably because in the latter case special precautions are observed.

Apepox.—The monkey appears to be susceptible both to smallpox and vaccinia. Zuelzer claims that he produced true variola in monkeys by inoculation with the blood and crusts of human variola. Copeman has also succeeded in inoculating monkeys with the fluid from lesions of human smallpox. More successful inoculations have been carried out by Magrath and Brinckerhoff.[1] Usually the resulting eruption is limited to the sites of inoculation, but occasionally a generalized outbreak occurs which may cover the entire surface of the body. Inoculated smallpox in the monkey is, however, seldom fatal. The monkey can be rendered insusceptible to smallpox by previous vaccination.

It is claimed that in the tropics apes sometimes die in large numbers of natural smallpox.

Anderson, of Glasgow, states that while smallpox was raging with great violence at St. Jago, on the west coast of New Grenada, monkeys were attacked with the disease in the forests near David, 60 or 70 miles away. Dying and dead monkeys were seen on the ground covered with perfect pustules of smallpox, and several ill monkeys were seen on the trees moving about in a sickly manner. In the course of a fortnight one-half of the inhabitants of the town of David were stricken with smallpox.[2]

Smallpox in the Camel.—In the province of Lus, in Beloochistan, the camels are said to be subject to a disease called "photoshootur," or the smallpox of camels. This disease is said to be communicable to the camel milkers and is alleged to protect them against smallpox.[3]

[1] Jour. Med. Res., February, 1904.
[2] Quoted by Atkin, W.: Practice of Medicine, 1868, p. 258.
[3] Quoted by Seaton: Indian Jour. Med. Sci., October, 1839.

CHAPTER IV.

SMALLPOX.

Synonyms.—Latin, *Variola;* French, *La Petite Vérole;* German, *Blattern,* or *Pocken;* Italian, *Vajuola.*

Definition.—Smallpox is an acute infectious disease characterized by an initial fever of about three days' duration, succeeded by an eruption passing through the stages of papule, vesicle and pustule, ending in incrustation and leaving pits or scars, the fever either intermitting or remitting in the papular stage and increasing in the pustular stage.

Derivation of Name.—Some difference of opinion exists as to the derivation of the term variola. It is alleged by some that it was coined by the monks during the Middle Ages, and that it is the diminutive form of the Latin word *Varus* (a papule, pimple or tubercle), a word found in Pliny. Other writers, however, believe it to be derived from the word *varius,* which means spotted or variegated.

The Saxon equivalent *pocca,* meaning a bag or pouch, has given rise to the English *pock* and the German *Pocken.* Syphilis appeared in Europe about 1498 and caused some confusion of nomenclature, so that it became necessary to prefix the adjective *small* to the term *pock* or *pox,* in order to distinguish it from the great pox, or syphilis. The same change was made in French phraseology; so that at the present day variola is designated *smallpox,* or *la petite vérole,* and syphilis the *pox,* or *la vérole.*

History.[1]—It is claimed by some writers that the antiquity of smallpox dates back to the time of the Tsche-u dynasty in China, at a period not less remote than a thousand years before the Christian era. It is stated that temples were erected in honor of the disease, and the goddess of smallpox was thus glorified. Inoculation, or "sowing the smallpox," it would appear was practised in China at a very early period, the result being crudely attained by thrusting crusts into the nostrils.

Smallpox in America.—It is said that smallpox reached Mexico in 1518, having been brought by a negro slave who accompanied the troops of Cortez from Cuba. According to Toribió, it swept the country, destroying the lives of 3,500,000 people. De la Condamine states that whole tribes of Indians were exterminated, and in some places no one was left to bury the dead. The disease then reappeared at regular intervals of seventeen or eighteen years. In 1633 the Indians

[1] For a more extended account of the history of smallpox, see Welch and Schamberg, Acute Contagious Diseases, Philadelphia, Lea Brothers & Co., 1905.

of Massachusetts were attacked by smallpox and slain by the thousands. The disease first appeared in Boston in 1649.

Referring to the importation of smallpox into America, Gregory humorously remarks: "If America gave us, as people confidently say it did, the great pox, we have more than returned the compliment by introducing to her acquaintance the smallpox."

Period of Inoculation.—Inoculation was first practised in Constantinople about the year 1674. Dr. Timoni (1714), Dr. Kennedy (1715) and Dr. Pylarini (1716) wrote on the subject of inoculation, but the profession in England ignored the publications. It remained for the charming and accomplished Lady Mary Wortley Montague, wife of the British Ambassador to Turkey, to introduce inoculation to the European world.

The daughter of Lady Montague was the first person ever inoculated in England (1727), although her son had previously been inoculated in Constantinople. In the following year, after six condemned criminals had been successfully inoculated, the two daughters of the Princess of Wales submitted to the new process.

During the first ten years of its career inoculation met with great opposition. Later it became more firmly established, and was extensively practised in England up to 1800. It never, however, became popular on the Continent. The average death-rate from inoculation was about 1 in 300 cases, although it often rose above this. In 1798 Jenner announced his discovery of vaccination. In 1808 the inoculation of out-door patients was discontinued at the London Smallpox Hospital, and fourteen years later inoculation of in-door patients was abandoned. In 1843 Gregory wrote: "In 1840 the practice of inoculation, the introduction of which has conferred immortality on the name of Lady Montague, which had been sanctioned by the College of Physicians, which had saved the lives of many kings, queens and princes, and of thousands of their subjects during the greater part of the preceding century, was declared illegal by the English Parliament, and all offenders were sent to prison with a good chance of the treadmill. . . . Such are the reverses of fortune to which all sublunary things are doomed."

Inoculation was first practised in America in 1721. It was introduced into this country at the suggestion of the Rev. Cotton Mather, by Dr. Zabdiel Boylston, of Boston, who first inoculated his only son and then two negro servants. Before the practice was generally accepted, however, it was necessary to overcome here, as in England, much violent opposition.

The principal advantage claimed for inoculation was that smallpox thus produced was much milder in type than when the infection was received in the natural way; while the death-rate from smallpox was 1 out of every 3 or 4 persons attacked, it was, at the highest from the inoculated disease, not greater than 1 out 50, and sometimes as low as 1 out 300, the average death-rate being somewhere between

the two. Not only the number of deaths, but the marred visages of persons in every community, testified to the frequency of smallpox before the days of inoculation. Indeed, it was so prevalent in the Middle Ages as to lead to the common saying that "*from smallpox and love but few remain free.*" The disadvantage of inoculation was that smallpox produced in this manner, although milder in type, was just as contagious as when contracted naturally; hence, inoculation had the effect of keeping the disease almost constantly in existence.

Prevalence of Smallpox in the Prevaccination Days.—Smallpox was so universal a disease that Ben Johnson wrote of it:

> "Envious and foul disease, could there not be
> One beauty in an age and free from thee?"

Smallpox was mainly a disease of children in former times, and the adult population consisted for the most part of the survivors from an attack in childhood, therefore permanently protected. The disease was regarded as universal or almost universal.

According to Dr. Lettsom, most children in London had smallpox before the seventh year.

Juncker estimated that 400,000 smallpox deaths occurred year in Europe on an average, and that five-sixths of mankind were attacked. Many writers were of the opinion that every one was attacked sooner or later. King Frederick William III of Prussia, in a dispatch dated October 31, 1803, states that smallpox caused on an average 40,000 deaths year in Prussia.[1]

Smallpox in Royal Families.—As indicating the widespread prevalence of smallpox in the prevaccination era, we may point to the frequency of this disease among the members of royal families who had the best opportunity, by seclusion or removal to another locality, to escape the ravages of epidemic maladies.

The Stuarts, the House of Orange, the Bourbons and the Hapsburgs were particularly stricken by smallpox.

The Stuarts.—Two children of Charles I died of variola—the Duke of Gloucester, in 1660, and at a later period Mary, Princess of Orange, mother of William III of Orange.

Queen Anne, daughter of James II, was attacked in 1677 but recovered, bearing thereafter the disfiguring insignia of the disease. Her brother, the infant Duke of Cambridge, became infected and died. Some years later Anne's beautiful sister, Mary, wife of William III, and queen regent of England, died at the age of thirty-three years.

In 1712 her brother, James Francis Edward, called the Chevalier de Saint George, was stricken in France with smallpox. He recovered, but the attractive Princess Louisa contracted the malady and died. It is thus seen that all of James II's children suffered from smallpox, 3 of them losing their lives.

[1] The above statements are quoted from Edwardes' Smallpox and Vaccination in Europe, 1902.

House of Orange.—William III passed through a severe attack of smallpox just before the battle of Seneffe. Both his father and his mother had died of this disease at different periods.

The Bourbons.—Louis XIV bore upon his visage the marks of smallpox. In 1711 his only surviving son, Louis the Grand Dauphin, died of malignant smallpox. The beautiful Mlle. de Blois, the legitimized daughter of Louis XIV, and her equally attractive sister, the Princesse de Conti, both lost the freshness of their charm from smallpox. His weak and dissolute grandson, Louis XV, succumbed to smallpox at the age of sixty-four years (1774). Louis XVI and his brothers were then *inoculated* against smallpox.

The Hapsburgs.—Smallpox was the relentless foe of the Hapsburgs. Joseph I of Germany died of smallpox in 1711. Joseph II (son of Maria Theresa) lost two wives within four years from this disease. Maria Theresa contracted the cruel malady and lay for days between life and death. A nephew, Albert of Saxony, suffered an attack. Two daughters, the Archduchesses Elizabeth and Josephine, contracted the disease, the latter succumbing.

It is also stated that several Austrian archdukes fell a victim.

Smallpox extinguished the male line succession of the Romanoffs. Peter II, grandson of Peter the Great, died of smallpox on the day set for his wedding. Peter III, descended from the female line, contracted smallpox at a later date and recovered, only to die by the assassin's hand.

Other members of royal families succumbing to smallpox were Henry, Prince of Prussia, Maximilian, the last Elector of Bavaria, an Elector of Saxony and Queen Ulrica Eleanora of Sweden in 1741.

George Washington "was strongly attacked" by smallpox during his early manhood, while on a visit to the West Indies.

THE ETIOLOGY OF SMALLPOX.

That smallpox may prevail in the frigid climes of Greenland and in the torrid regions of Africa is evidence of the fact that conditions of soil or climate exert but little influence over the disease. Practically no civilized country on the globe has been exempt from the ravages of smallpox. It follows, like other transmissible diseases, the channels of trade and human intercourse. When the contagium of the disease is brought to an unprotected community there the malady takes root and spreads.

Susceptibility to smallpox is almost universal; but few persons can boast of natural immunity from this disease. Yet this individual peculiarity is occasionally encountered, as may be seen by reference to the history of the disease during the prevaccination period. Persons have been known to go through life constantly exposed to the infection without suffering from any manifestation of smallpox. It is said that Morgagni, Boerhaave and Diemerbroeck enjoyed this privi-

lege. It is not impossible that such immunity may have resulted from a mild attack of smallpox, from which such persons may have suffered *in utero*, even without their mothers having presented any manifestations of the disease.

Instances are recorded in which persons have resisted the infection when exposed in the usual manner, but have yielded to the disease by inoculation later in life.

Instances are met with, under rare circumstances, of apparently healthy persons resisting the infection of smallpox at one time and yielding to it at another. We will relate a case in point: In 1874 a colored man, aged thirty years, came under the care of Dr. William M. Welch, suffering from confluent variola. He stated that vaccination had been performed at different times during his life, but never successfully: In 1871 he belonged to a crew of a sailing vessel in which several cases of smallpox occurred, and his duties required him to frequently come in contact with those who were ill, yet he did not take the disease. He was vaccinated at that time, but, as before, without result. When he fell ill with variola three years later he was unable to account for the source of the infection. The attack proved fatal.

In the days when inoculation was extensively practised it was noticed that some persons exhibited a temporary insusceptibility to the infection. Gregory informs us that Woodville found 1 out of every 60 children, and 1 out of of 20 adults to be temporarily insusceptible to inoculation. Experience demonstrates that the susceptibility to smallpox may at one time be diminished and at another greatly increased.

The existence of acute and chronic infectious diseases is said by some writers to temporarily lessen the susceptibility to the infection of variola. Curschmann asserts "That for an individual suffering from scarlet fever, measles or typhoid fever there is during the entire duration of the affection only a very slight susceptibility to an attack of variola." He observed in the hospital at Mayence (where the smallpox building was near the general wards) that variolous infections never took place during the course of the typhoid process. A considerable number of typhoid convalescents, however, were attacked after their temperatures had become permanently normal. He was led to this conclusion from the fact that the interval between the time of the subsidence of the fever and the beginning of the initial stage of variola corresponded to the longest period of incubation that is encountered, namely, fourteen to nineteen days. There is no doubt, however, that the variolous infection does frequently occur during the existence of an acute disease, only the incubation period in such cases is often greatly prolonged. Smallpox has been known to exist with the acute exanthemata, particularly scarlet fever and measles. We have seen unprotected children, while suffering from measles in its most acute stage, exposed not longer than two minutes to the infection of variola, sicken with the disease after the usual incubation period. We have also observed this sequence of events to develop in connection with

a diphtheria patient. In at least a half dozen instances we have noted the coexistence of smallpox and scarlet fever. Chronic infectious maladies, such as syphilis and tuberculosis, not infrequently exist in individuals who are attacked by smallpox.

Recurrent Smallpox (Second Attacks).—The susceptibility to smallpox is removed by vaccination, but frequently reappears to a greater or less degree in a variable period of time. So also one attack of smallpox does not invariably protect the individual for the remainder of his life against a future attack. It is undoubtedly the rule that a person does not suffer from the disease more than once, but well-authenticated cases of second attacks are recorded. Indeed, some writers allege that the predisposition to smallpox in some persons is so strongly marked as to render them susceptible to the infection more than twice, even as often as five or six times. The authenticity of reported cases of this kind, however, is not to be taken for granted, but accepted with extreme caution, as there are many sources of error.

Jenner, who closely studied casual and inoculated smallpox for more than thirty years, was very positive in his views as to the permanency of the protection which one attack of the disease conferred, and it was doubtless his positive convictions on this point that led him to announce his oversanguine belief in the permanency of the vaccine influence.

Gregory, who enjoyed unusual opportunities for studying variola, was very incredulous on the subject of recurrence of the disease. Most of the reported cases which he was called upon to examine he found incorrectly reported. Echthyma, pustular syphilis and particularly varicella, he states were fruitful sources of error. But few patients claiming to have had smallpox previously came under his care as physician to the Smallpox Hospital of London for more than twenty years, and of these few only a very small fraction could stand the test of rigid scrutiny. Koch states that in the great epidemic of 1871–1872, among 12,000 cases of smallpox in South Germany, no second attack occurred.

Marson is responsible for the statement that during the one hundred and nineteen years since the founding of the London Smallpox Hospital there is no record of a patient having been admitted twice, suffering from smallpox. He reports, however, the following interesting instance of recurrent smallpox: "An Irishman, the son of a medical officer of the army, who had been vaccinated in infancy by his father, and who had a large cicatrix remaining from the vaccination, and who was attended by his father for smallpox in early life and bore decided pits of the disease, in 1844, at twenty-three years of age, was admitted to the Smallpox Hospital with severe confluent smallpox, of which he died." Marson believes that exposure for a time to a great change of climate, either hot or cold, seems to predispose the constitution to receive a second attack of smallpox.

It is said that Grossheim observed a light form of variola in a patient three months after the first attack, but this peculiar case was the only

instance of recurrence which he noted among 22,641 in the German Military Hospitals.

Dr. Welch and one of the authors saw a number of patients who claimed to have had smallpox previously, but only a very few were able to show anything like characteristic pitting; all of those who did show such evidences of a previous attack had the disease the second time in the mildest possible form—so mild, indeed, in some instances, as to be scarcely recognizable, the eruption being either arrested in the papular or in the vesicular stage. We have never seen an unmodified or even a severe case of smallpox occur in a person who was deeply and characteristically pitted from a previous attack.

Two cases of undoubted second attacks, however, came under our observation: one was a woman, aged twenty-nine years, who had a severe attack of smallpox at the age of one and a half years. The patient's face was fearfully scarred and seamed. The second attack was extremely mild, there being but two hundred modified lesions upon the entire cutaneous surface.

The second case was a man, aged fifty years, who had his first attack in Scotland at the age of three years; at this time five of his brothers died of the disease. The patient presented a number of superficial pits about the face. The second attack was accompanied by a fairly abundant eruption, but the lesions were distinctly modified. He had never been vaccinated.

The evidence relied upon to prove the occurrence of second attacks is usually obtained from patients themselves, inasmuch as it is exceedingly rare for a physician to observe two distinct attacks of smallpox in the same individual. During a period of thirty-four years, in which time more than 9000 cases of smallpox were treated in the Philadelphia Municipal Hospital, no person had been twice admitted suffering from the disease. In view of all that has been said, it is probable that second attacks of smallpox are much rarer than is generally supposed.

Age.—Age cannot be said to influence the predisposition to the disease, as it is naturally present at all periods of life, from earliest infancy to extreme old age. If aged persons are found less susceptible at all, it is because of the prophylactic power of vaccination. While nursing infants under six months of age commonly resist the infection of measles and scarlet fever, they are nearly always susceptible to the infection of smallpox. Even the fetus *in utero* is not exempt from the danger of an attack when a pregnant woman suffers from the disease. The variolous process in such a patient is exceedingly likely to excite abortion or premature delivery, and the fetus, or child, may show evidence of the disease in the form of an eruption. Such evidence has been observed as early as the fourth month of fetal life; we have ourselves seen a sparse eruption in the vesicular stage upon a fetus expelled at four months. We can also recall several instances of children born at or near term with the smallpox exanthem present; in one case it had advanced to the pustular stage and the child was born dead. In

another case the child was born at eight months, with the variolous eruption just appearing, and died when the pustular stage was reached. It is an acknowledged fact that a woman, though personally immune, may give birth to a child suffering from smallpox; it is not improbable in such cases that the mother has passed through a *variola sine exanthemate*.

Sex.—The predisposition to smallpox is not influenced by sex. Of course in every epidemic a larger number of male patients is received into smallpox hospitals than females. This is manifestly due to the fact that men are, by reason of their daily occupation, exposed to a greater extent to the infection.

During the epidemic of 1901–1904 quite a large number of motormen and conductors employed on the street railway were admitted into the hospital. Women, on the contrary, as a result of the greater amount of time spent in-doors, are less subjected to contact with infected individuals. Of 7204 cases of smallpox treated up to 1903, in the Philadelphia Hospital for Contagious Diseases, 4598 were males and 2606 were females. Under the same conditions, however, males and females are equally susceptible to the disease.

Race.—There is some difference of opinion concerning the influence of race upon susceptibility to smallpox. Most authors state that the predisposition to variola is more marked among the dark-skinned peoples, particularly the negro race. There is no doubt that when smallpox prevails epidemically in this country the proportion of deaths to cases is greater among the negro than among the white race; but this we believe is owing to the fact that there is greater neglect of vaccination among the former. In our experience the unvaccinated cases of each race have perished in about the same proportion.

The aboriginal races appear to receive smallpox in a most virulent form and with fearful mortality. When smallpox first gained entrance into Mexico it spread like wild-fire, exterminating tribes to such an extent that frequently not sufficient survivors were left to bury the dead. Smallpox has also proven itself frightfully fatal among the Indian tribes of North America. In Quito 100,000 natives were destroyed.

Season.—Rhazes, the Arabian physician, who wrote in 900 A.D., says: "I am to mention the seasons of the year in which the smallpox is most prevalent, which are the latter end of the autumn and the beginning of the spring, and when in the summer there are great and frequent rains with continued south winds, and when the winter is warm and the winds southerly."

Sydenham said that when a smallpox epidemic is mild it begins about the vernal equinox (March 25); but when of an extended and dangerous kind it begins in the month of January. These generalizations are scarcely borne out by the history of smallpox visitations.

In England the smallpox appears to be most prevalent during the

first six months of the year; according to Parkes,[1] the average London mortality from smallpox, from observations covering a long period of years, is greatest during the first six months of the year, rising to a maximum toward the end of May and falling through June, until it descends to the mean line, where it fluctuates during the last six months, to rise again in December or January.

In Philadelphia smallpox during epidemic prevalence almost invariably increases in the fall of the year, beginning with the month of September or October. The number of cases then steadily rises, reaching the maximum during the months of December, January and February, and then declining month by month until July and August, when the minimal incidence is reached.

While in temperate climates smallpox is essentially a *cold-weather disease*, the reverse is said to be true in tropical countries. The malady in such localities is alleged to be at its worst in the hot months and to improve during the cooler season.

The following tables indicate the monthly number of smallpox patients reported during the three large epidemics that have occurred in Philadelphia in the last half century:

	1871.	1872.
January	13	3130
February	6	1794
March	4	1247
April	8	587
May	9	401
June	11	208
July	15	66
August	58	30
September	111	13
October	1628	18
November	2944	11
December	3307	10
	8114	7515
Total		15,629

	1880.	1881.	1882.	1883.	1884.	1885.
January	47	885	321	152	30	3
February	78	711	284	131	25	1
March	39	575	198	91	21	0
April	25	658	150	76	31	3
May	28	523	106	60	23	5
June	32	406	64	45	20	2
July	30	241	36	34	6	0
August	96	155	18	45	7	0
September	75	208	30	57	5	0
October	301	186	43	27	2	0
November	382	224	47	35	6	0
December	719	336	127	37	11	0
	1866	5108	1424	790	187	14
Total			9389			

[1] Hygiene and Public Health, London, 1901.

	1901.	1902.	1903.	1904.
January	1	433	126	317
February	1	314	125	148
March	5	186	136	133
April	17	111	68	100
May	10	84	125	85
June	9	54	151	17
July	14	47	137	2
August	52	12	85	2
September	116	15	42	0
October	247	17	93	3
November	304	11	242	8
December	384	58	365	2
Total	1160	1342	1695	817
		5014		

The above tables show a remarkable uniformity in the rise, culmination and decline by month of the three epidemics. In all three the epidemic actually began in August and continued to increase throughout the autumn, reaching a culmination in December and January. A gradual decline then occurred during the spring, falling to the lowest level during the summer months.

It would appear from a study of these three visitations that the maximum intensity of epidemics in this city is reached during the winter months of the first year, particularly December and January. When the epidemic extends throughout several winters, while the highest level of each year is reached during the cold season, there is, as a rule, a gradual decline from winter to winter until the epidemic dies out.

This is well illustrated in the epidemic beginning in 1880. The epidemic beginning in 1901 is, however, an exception to this generalization. During the winter of 1902–1903 it looked as if the epidemic was dying out, but during the following winter (1903–1904) it acquired renewed force and almost equalled, as regards the number of persons attacked, its extent in the winter of 1901–1902. Indeed, during the calendar year of 1903 there were actually more cases of smallpox in the city than during the preceding years.

In the visitation of 1871–1872 the force of the epidemic was expended during the year from August, 1871, to August, 1872, when the disease was practically exterminated. Of the 15,629 cases which occurred in the two years 15,476 developed from August to August.

In the epidemic which began in 1880 and continued for four or five years, of the total number 9389 cases, 5502 occurred during the first year beginning with August.

Even in the epidemic beginning in 1901, which exhibited a recrudescence in 1903, the largest number of cases (2332) developed within the year from August, 1901, to August, 1902.

The Infection of Smallpox.—No one would deny at the present day that smallpox is due to a specific microörganism. There is, furthermore, no doubt that the disease is spread by means of this organism,

which is reproduced in every patient. A small quantity of the fluid from a pustule inoculated into an unprotected person gives rise to the disease; this is conclusive proof of the fact that the germ is resident in the lesions. It is also present in the exhalations from the patient and in the blood. Zuelzer proved that it is contained in the blood by successfully inoculating a monkey with blood taken from a smallpox patient. It would appear from the experiments of the older writers that the physiological secretions and excretions, the saliva, sputum, urine, feces, etc., are not in themselves infectious; when, however, they become contaminated with particles derived from the skin and mucous membrane lesions they doubtless acquire an infectiousness.

The contagium emitted by a patient is most intense in his immediate vicinity, but it may be transported in an active state for some distance by the atmosphere. If a susceptible person should enter a poorly ventilated small apartment containing one or more severe cases of smallpox, infection would almost certainly occur, while if the apartment were large and well ventilated and the cases few and mild, the risk of infection would be diminished; if he should approach equally near the same patient in the open air the risk would be still less.

Infectious Period of Smallpox.—Smallpox is undoubtedly infectious in all stages characterized by symptoms. It is alleged by some that the disease is even infectious during the period of incubation, but we think there is very little reason to believe that such is the case. It is possible, however, that the blood of an individual at this stage might convey the infection if it were introduced into the system of a susceptible person.

Schafer, quoted by Curschmann, reports an interesting case in this connection: "In the Charité Hospital of Berlin small pieces of skin were taken for transplantation upon other individuals from the amputated arm of a person who, before and at the time of the amputation, did not manifest the slightest symptoms of general disease. Several hours after the amputation the patient was attacked with violent fever, followed two days later by the eruption of smallpox. One of the individuals upon whom the transplanted skin had been placed was attacked by variola on the sixth day after the operation. The three others remained exempt.

The disease is least infectious during the initial stage and most highly so during the suppurative and early period of the desiccative stages. The scabs are unquestionably infectious, and as long as these remain on the skin the patient should be regarded as dangerous to the community. Apart from the experience of modern observers, evidence of the infectiousness of the crusts is found in the ancient custom in vogue among the Chinese of inoculating smallpox by inserting the crusts in the nose.

Even after death the body appears to retain the power of transmitting the contagium. This fact has been demonstrated more than once where public funerals have not been interdicted, and where bodies of

persons who have died of smallpox have by accident found their way into dissecting rooms.

Austin Flint records an interesting case in which the disease was spread by a cadaver:

"During the winter of 1848–1849 a young man, a member of the medical class of the New York University, died suddenly and unexpectedly in the night, under the care of a physician who had not thought him seriously ill. I was invited to the autopsy, and observed when the corpse was uncovered a few dark-red spots on the surface, which were supposed to be petechial, the principal symptoms of his attack having been gastric, with great debility, as we were informed. The coffin was taken to a New England village for burial, where at the funeral some of the relatives approached and opened it to see the face of the deceased before it was inhumed. Of this number 8 were attacked with smallpox, no other person in the neighborhood being assailed."

The infection of smallpox may be conveyed in the following ways:

1. Through direct exposure to the patient or to infected secretions and excretions.
2. Through contact with objects which have been infected by the patient, for example, sick-room articles.
3. Through infection carried in the clothing or on the person of healthy individuals.
4. Through air transmission.
5. Through transmission by insects and domestic animals.

Infection Through Direct Exposure to the Patient.—The vast majority of cases of smallpox result from exposure to individuals suffering from the disease. Smallpox is the most typical example of the contagious or catching disease. The briefest possible exposure on the part of a susceptible person will suffice to produce the disease. Many victims never discover the source of their infection; this is not so surprising when we appreciate the fact that the patient may impart the disease before the appearance of the eruption. That smallpox may be transmitted during the initial stage is undoubtedly proven by the records of cases in which the infection was received from individuals suffering from *variola sine exanthemate*. Persons are also frequently exposed to patients suffering from extremely mild and unrecognized forms of smallpox. The patients may not deem themselves ill and may after the initial illness continue their daily labors, in this manner unconsciously endangering the health of those with whom they come in contact. We recall, during the mild epidemic of smallpox of some years ago, a negro who drove a carriage along one of the principal thoroughfares of this city, who, though in the pustular stage of smallpox, did not feel sufficiently ill to remain at home. Time and time again have we been informed by patients that they came to the hospital in street cars. Some, too, admitted having travelled on the railroad from cities more or less distant while suffering from the disease in its early stages.

The fact is conclusively proven that the degree of severity of the attack produced in the second person bears no relationship to that in the infecting individual. We recall the case of a fatal hemorrhagic smallpox in a pregnant woman who received the infection from her father-in-law, whose attack was so mild as to escape unrecognized.

A robust constitution is no safeguard against variolous infection; in fact, some writers consider persons in good health more susceptible to the disease, on the same principle that ruddy children take vaccination more easily than weaklings.

Sometimes extensive epidemics arise from the importation into the community of a single patient suffering from the disease. One of the most remarkable instances of rapid diffusion of smallpox is the epidemic in Montreal in 1885, recorded by Osler. The city was visited by smallpox from 1870 to 1875, after which it died out, owing to vigorous vaccination and the exhaustion of suitable material. For ten years the city remained free of the disease. The French Canadians, being as a class opposed to vaccination, a large unvaccinated population grew up in this period. On February 28, 1885, a Pullman-car conductor, who had arrived from Chicago, where smallpox was prevalent, was removed to the Hôtel Dieu, the civic smallpox hospital being at that time closed. Isolation was not practised, and as a result a servant in the hospital contracted the disease and died. After this occurred, "with a negligence absolutely criminal, the hospital authorities dismissed all patients who presented no symptoms, who could go home." The disease spread like fire in dry grass, and within nine months 3164 people die of smallpox.

Infection Through Sick-room Objects.—While the contagium of smallpos is perhaps more commonly conveyed from person to person through the atmosphere, this is by no means the only medium of infection. The infecting germs become attached to all objects in the immediate vicinity of the patient, and cling to them for a variable period of time. Objects which have a rough, shaggy surface, such as blankets, woollen clothing, etc., not only become more intensely infected, but hold the infection much longer than smooth objects. Woollen garments closely packed and excluded from the air as completely as possible have been known to retain the infection for many months or even years. If, however, such garments be freely exposed to the atmosphere and sunlight, the contagium will soon be destroyed. Of course it may be destroyed at once by disinfecting agents.

Infected objects may convey the contagium over long distances, even over many hundreds of miles. In 1898 we saw a case of smallpox in this city in which we believe the infection was received from a bale of cotton brought from the South. Smallpox was prevalent in the cotton-growing districts of the Southern States, and was of such a mild type that the negro patients would frequently be in the fields gathering cotton while the eruption was developing or the scabs dropping off.

The case occurred in a man employed in a Philadelphia mill where

cotton goods were manufactured, and which had received cotton from the South. At the time no cases of smallpox were present in Philadelphia or its vicinity, nor had there been for a period of two or three years. The man had not been out of the city for a long time. In seeking for the source of the infection we could arrive at no other conclusion than that it had been derived from a bale of cotton.

Infection Carried by Healthy Individuals.—Not only objects in the room, but also healthy persons whose duties require them to come in contact with the sick, may be the means of communicating the infection. The infection may adhere to the hair, the hands and other parts of the body of the attendants, but the chief danger is from their clothing

That healthy individuals may carry the infection has been conclusively demonstrated to us. We have, on a number of occasions, had brought into the hospital infants suffering from smallpox who had not been out of their homes and who lived in neighborhoods free of the disease.

Great caution should be observed by physicians, nurses and others in attendance upon smallpox patients. The exercise of proper care will reduce the chances of carrying infection to a minimum. One of the writers has come in contact with thousands of smallpox patients, but by the exercise of great care has never to his knowledge conveyed the disease to a single individual.

Air Transmission of Smallpox Infection.—The contagium given off from a patient suffering from smallpox consists of particulate matter, capable of surcharging the atmosphere of the sick-room. The older writers believed that the sphere of contagious influence of smallpox was extremely limited.

English physicians some years ago devoted considerable study to the determination of the striking distance of the disease.

In the epidemic of 1881 Mr. W. H. Power,[1] after excluding all possible infection through ordinary intercourse, formulated an hypothesis of atmospheric convection of the smallpox poison. He assumed that smallpox infective material was "particulate," and that certain favorable conditions could disseminate such particulate matter over an area of $\frac{1}{4}$ or $\frac{1}{2}$ mile.

The particulate matter, or infectious dust, may be held in suspension in the water particles in the air, in fog and mist, and may be driven by air currents and deposited at some distance. During periods of stillness of the air about the hospital the infection is taken up and then wafted by the winds. The absence of ozone in the atmosphere is also said to be favorable to spread of infection. Periods of small movement of air and absence of ozone are said by Mr. Power to have preceded each of the more notable epidemic extensions in the neighborhood of the Fulham Hospital.

Parkes[2] says: "The exceptional incidence of smallpox in the imme-

[1] Supplement to Local Government Board, 1880–1881, also 1884–1885.
[2] Hygiene and Public Health, London, 1901.

diate neighborhood of some of the London Smallpox Hospitals can admit of but one explanation, viz: that when a sufficient number of cases in the acute stages are collected together in one building on a small area of ground the hospital becomes a center of infection to the surrounding neighborhood" (Fig. 33).

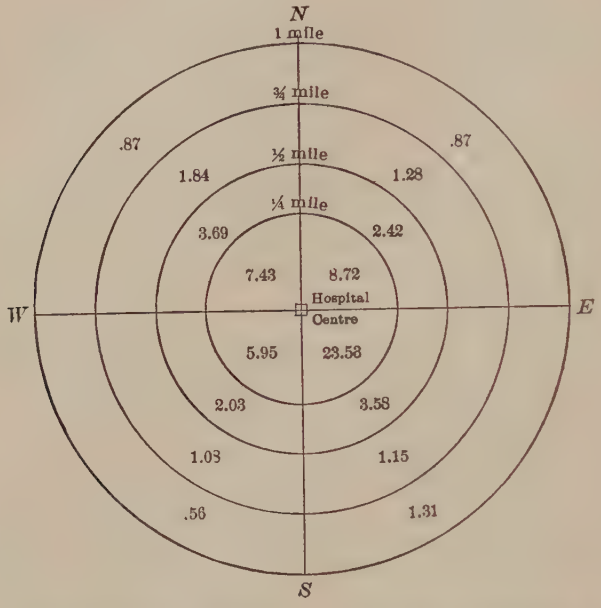


FIG. 33.—Special area around Fulham Hospital divided into sections of ¼, ½, ¾ and 1 mile radii, showing in the different areas the number of houses (out of every 100) invaded by smallpox from May 25, 1884, to September 26, 1885. Between *N* and *W* the hospital was greatly isolated from traffic because of few roadways. Belt of houses between *W* and *S* comparatively narrow. Between *N* and *E* houses few within ¼ mile: beyond they completely encompass the hospital. The so-called special area was within 500 feet from the hospital centre.

"As regards the number of cases aggregated in a hospital necessary to enable it to exert an influence on the surrounding neighborhood, Dr. Power's reports of 1884–1885 show that this influence was exerted when the number of acute cases had been restricted to 20, while on one occasion he found the excess of smallpox in the neighborhood of the Fulham Hospital was quite remarkable at a time when the total admissions to the hospital had not exceeded 9, only 5 of these being cases in an acute stage."

Mr. A. W. Blyth[1] remarks: "The usual spread of smallpox is from person to person, but, from inquiries which have taken place as to the influence of smallpox hospitals upon a surrounding population, it is certain that the infection can strike at a distance.

[1] Manual of Public Health.

The influence of the Sheffield Hospital in the epidemic of 1887–1888 could be distinctly traced for a circle of 4000 feet; the following percentages of households attacked at successive distances from the hospital are given in the original reports by Dr. Barry,[1] inspector of the Local Government Board for England:

	Percentage of houses attacked at varying distances from Sheffield Hospital.
0 to 1000 feet	1.75
1 to 2000 "	0.50
2 to 3000 "	0.14
3 to 4000 "	0.05
Elsewhere	0.02

The possibility of smallpox spreading by aërial infection increases greatly both the hospital difficulty and that of individual isolation.

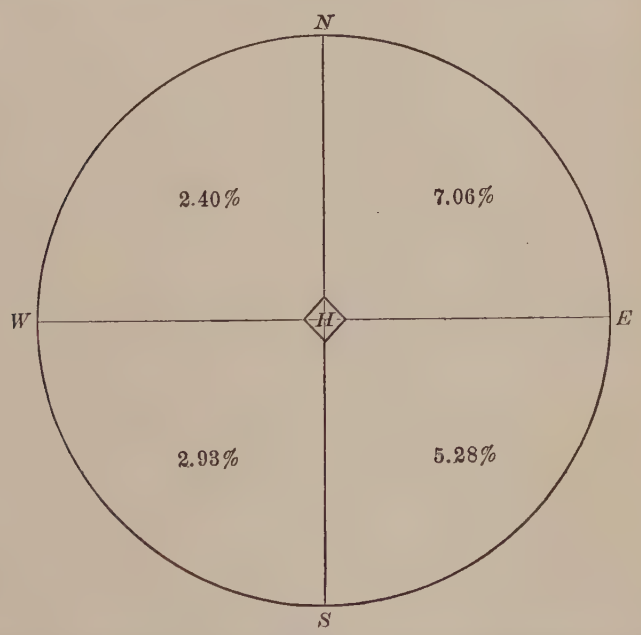


FIG. 34.—Diagram showing the influence of the wind in disseminating smallpox. (Evans.)

Evans,[2] from observation of a smallpox epidemic at Bradford, came to the same conclusion as Barry. During the year 1893, 626 domiciles were attacked by smallpox within a radius of 1 mile of the Bradford Fever Hospital.

Within the $\frac{1}{4}$-mile circle about the hospital the rate was 10.4 per

[1] Report of an Epidemic of Smallpox at Sheffield, 1887–1888, London, 1889.
[2] Quoted by Moore: Brit. Med. Jour., 1894, ii, 356.

cent; between the ½-mile and the ¾-mile, 2.1 per cent. Evans believes that the extensive prevalence of smallpox within the special area about the hospital is to be explained on the grounds of aërial transmission of infected material from the wards of the hospital.

This view he believes is confirmed by a study of the direction of the prevailing winds during the year 1893.

"These figures," he says, "are readily explained by the fact that on two hundred and fifty days of the year the prevailing winds were westerly and only on eighty-three was the wind persistently from the east."

Thresh,[1] from a study of smallpox outbreaks in the neighborhood of the smallpox hospital ships in the Thames River, says: "The extent of the area around a smallpox hospital which may be affected directly and indirectly by the hospital is apparently much larger than has heretofore been supposed. In the case of the ships lying off Purfleet the influence is probably being felt at a distance of fully 3 miles, and the presence of a belt of water ½ mile in width is powerless to arrest the contagion.

He further says: "The hospital ships were placed opposite Purfleet in 1884, and since that time there has been an excessive prevalence of smallpox in the Orsett district, and especially in that portion lying nearest the ships. Prior to these floating hospitals being established near Purfleet, smallpox was little more prevalent in the Orsett district than in the remainder of the country, and only one-third to one-fourth as prevalent as in the metropolis.

"The change since then has been most marked: From the same basis the disease has been seven times more prevalent in Orsett than in the remainder of the country, and two and one-half times more prevalent than in London."

Dissenting Views as to the Atmospheric Transmission of Smallpox Inspection.—Certain writers dissent from the view above expressed as to the aërial convection of smallpox.

Seaton[2] believes that no adequate evidence has been adduced to prove aërial convection for hospitals situated in sparsely settled districts.

He speaks of an instance which came under his observation in which a number of unvaccinated children living within a stone's throw of a smallpox hospital did not take the disease until a child sick with smallpox was brought to the house, and the unvaccinated children thus directly exposed to the contagion. This was regarded as evidence that the contagion of smallpox does not extend to any considerable distance through the air.[3]

Savill[4] holds "That fresh air, being itself one of the best natural germicides, is very unlikely to become a vehicle for the conveyance of microbes, and that on *a priori* grounds, therefore, we would not

[1] Lancet, February 22 and 26, 1902.
[2] Brit. Med. Jour., 1896, p. 582.
[3] Ibid., August 5, 1882.
[4] Wallace, J.: Smallpox, London, 1902.

expect the germs of smallpox to be carried beyond the limit of an ordinary room."

He carefully investigated the epidemic of smallpox at Warrington in 1892–1893, which he reported to the Royal Commission on Vaccination, and concluded that there was no need to assume a theory of aërial convection to explain the spread of the disease.

Wallace,[1] in discussing this epidemic, comments on some of the observations presented in Savill's report. He points out that aërial convection would not explain the spread of the epidemic, for: (1) The numbers of infected houses do not work out in perfect keeping with a theory of proportionate distances from the hospital as a center, and (2) the largest proportion of infected houses is not to be found in the quadrant opposite the prevailing winds.

Experience of Philadelphia During the Epidemic of 1901 to 1904.—During the years 1901, 1902 and 1903 there occurred in the city of Philadelphia 3989 cases of smallpox. Throughout the entire epidemic the twenty-eighth ward, in which the Municipal Hospital was located, furnished by far the largest number of smallpox patients. Next to this ward, in smallpox incidence, came those adjoining it. In the twenty-eighth ward there were 144 cases of smallpox per 10,000 of population. In the entire city, exclusive of this ward, the rate was 29 per 10,000 of population. The twenty-eighth ward and several of the neighboring wards, representing 26.71 per cent of the population, contained 53.67 per cent of the smallpox cases.

Although we were at first skeptical concerning the aërial transmission of variolous infection from a smallpox hospital, the preponderating incidence of smallpox in the Municipal Hospital district and adjoining wards throughout the entire epidemic has forced us to accept this mode of dissemination of the disease as established.

Transmission by Insects and Domestic Animals.—Researches within recent years have established the fact that insects may, in a number of diseases, directly convey infection to the human subject. The infective agents may undergo evolutional development in the insect, the creature thus acting as an intermediate host, or it may be carried upon the wings and feet.

In the warmer months of the year the common house fly abounds in the wards of hospitals. This insect is essentially a scavenger, and is particularly attracted by foul-smelling pus. It is a common sight in the summer season to observe swarms of flies foraging upon the purulent material upon the faces and hands of smallpox patients, the wings and feet of the insects being frequently bathed in the contents of the ruptured pustules.

We have undertaken investigations to determine whether or not the flies swallow the purulent material. Repeated microscopic examinations of the intestines of flies caught in the vicinity of smallpox patients

[1] Wallace, J.: Smallpox, London, 1897, p. 1680.

demonstrated the presence of an abundance of streptococci and staphylococci, which are the predominating organisms in the late variolous pustules. These germs did not appear to be digested, for they took the ordinary stains well. The intestines of flies caught about ordinary households, on the other hand, contained no germs of this character, and, indeed, often no germs at all. Inasmuch as the causal parasite of smallpox is resident within the pustules, it is reasonable to suppose that it also is swallowed by the fly.

It is obviously impossible to present proof that flies transmit the infection of smallpox; but that they are capable of doing so appears strongly probable. A fly carrying upon his feet or wings the *contagium vivum* of variola would, on alighting upon a susceptible individual, offer every opportunity for infection. It is also possible for the swallowed germs to be deposited in the form of excrement upon the face or hands of an unprotected person.

The ordinary house fly, or *Musca domestica*, is, owing to the conformation of the mouth parts, incapable of biting. A form of stable fly, the *Stomoxys calcitrans*, frequently found in houses, does, however, pierce the skin. Such a fly might readily carry the infection of smallpox into the skin in the act of biting, and thus give rise to an inoculation form of smallpox.

To what extent flies and other insects contribute toward the spread of smallpox cannot be determined. As flies are capable of travelling a considerable distance, some cases of smallpox of mysterious origin might be explained through their agency.

That the transmission of smallpox through the medium of flies, however, is not an important factor in epidemics is evidenced by the fact that the disease spreads most in our climate in the cold months, when flies are absent, and least in the hot months, when they are abundant.

It is quite conceivable that dogs, cats and other domestic animals occupying domiciles in which smallpox exists may carry the contagion of the disease in their fur. The closer the contact of such animals with the variolous patient, the greater is the likelihood of particulate infection being transferred. The roving of these animals might play some role in the dissemination of the disease within limited areas.

THE SYMPTOMATOLOGY OF SMALLPOX.

Period of Incubation.—From the moment that the microparasite of smallpox is received into the system certain subtle and unknown processes begin which, in the course of a more or less constant period of time, culminate in active clinical manifestations. To this latent breeding stage the term "period of incubation" is applied. The time elapsing between the reception of the variolous poison and the outbreak of the disease can occasionally be determined with a considerable degree of accuracy. This is more easily accomplished in sporadic cases, where an individual has been exposed but once and for a brief period of time.

Where the exposure is frequent or extends over a long period it is difficult to divine the exact moment when the infection is received. When the disease prevails in epidemic form it is not impossible for an unknown exposure to precede the one of which the individual has knowledge; in such cases the computed period of incubation would appear to be unusually short. Erroneous calculations of the duration of the period of incubation have doubtless arisen from failure to recognize this fact.

In the majority of cases in which we have had the opportunity of carefully studying the incubation stage, we have found it to be ten to twelve days, and we would, with other writers, regard this as the normal period. In a few instances it is true we have known persons to fall ill with smallpox after the raising of a two weeks' quarantine in houses in which they were confined and in which smallpox had existed. We have also been able in a few cases to reckon with tolerable certainty a period of incubation of sixteen days, the eruption appearing on the eighteenth. Some writers have recorded instances in which the incubation period has been prolonged to twenty days. With the "mild type" of smallpox the incubation period may be even longer. On the other hand, we have known a young physician, exposed to smallpox, to develop the first symptoms at the end of five and a half days, and the eruption at the termination of ten and a half days. Ordinarily, however, the period is seldom less than eight days or more than fourteen.

The incubation period is ordinarily not characterized by any active symptoms. Patients usually pursue their daily occupations ignorant of the fact that there is developing within them a dread disease. There are, however, frequent exceptions to this rule. It is not rare for patients to lose their appetite and complain of lassitude, chilliness, headache, gastric uneasiness, etc. These symptoms, when they occur, are commonly noted during the last few days of the incubation period. They may, however, develop as early as a week before the invasive chill. Now and then a patient will complain of slight sore throat during the last days of this stage.

The Stage of Invasion, or Initial Stage.—This stage is frequently ushered in with suddenness and with considerable violence. The earliest symptom is most frequently a *chill*. This may be severe enough to be accompanied by chattering of the teeth, or it may consist of a succession of creepy sensations scarcely sufficient to attract the patient's attention. Synchronously with the chill or immediately following it the *fever* appears. The temperature on the first day often rises to 103° or 104° F., and on the second and third day, with perhaps the exception of slight morning remissions, it rises still higher, frequently reaching 105° F., and in some cases even 107° F. The elevation of temperature is usually sudden; in but few diseases does it rise so quickly from the normal to a high degree. Even in varioloid the early symptoms are not infrequently equally severe, although occasionally

they are so mild as to escape attention. But the eruption of unmodified smallpox seldom, if ever, appears without being preceded by a well-marked invasive stage.

During the continuance of the fever the skin is hot and sometimes dry. Profuse sweating, however, is by no means uncommon; this is apt to come on in the evening.

The *pulse*, as a rule, is full, tense and rapid, its frequency generally corresponding with the temperature curve. In adults it varies between 100 and 130, while in children it not infrequently reaches 160. In some cases the pulse during the initial stage will be found to be relatively slow and entirely disproportionate to the height of the fever. We have on a number of occasions noted a pulse of 90, 80 and even 70, with a temperature of 104° or 105° F. These cases were seen in the hospital on the first and second day of the eruption; consequently we are not able to state whether this pulse-rate was present at the onset of the initial symptoms.

The respirations are almost always increased in frequency, especially when the temperature is excessively high. Prostration is often extreme, being out of all proportion to the length of the illness. Strong and robust patients are frequently unable to stand without support, and when in the upright position soon become pale and liable to be attacked by vertigo or syncope. Thirst is great, the lips and tongue are parched and dry and there is complete loss of appetite.

Constipation is a common symptom and is apt to persist throughout the course of the disease. The tongue is usually coated with a thick, yellowish covering and the breath is heavy and offensive. According to some authors, the odor from the body of a patient at this stage of the disease is so peculiar and distinctive as to make it possible for the diagnosis of smallpox to be made by this symptom alone. We must confess that our olfactories have not acquired the degree of acuteness to detect such an odor.

Irritability of the stomach is a very frequent manifestation. Occasionally the first symptom noted by the patient is severe and persistent vomiting. In such cases the disease has on more than one occasion been regarded as gastritis. The *vomiting* often continues for two or three days. It is apt to be accompanied by marked tenderness and pain in the pit of the stomach. The irritability usually ceases when the eruption appears. When it continues longer it should be viewed with some solicitude. Especially in hemorrhagic smallpox is this symptom, together with epigastric pain, apt to be distressing and prominent. Nausea and retching are present in some cases without actual emesis.

Headache is the most prominent among the early nervous symptoms. It usually follows shortly after the chill, but in a certain proportion of cases it precedes it, being not infrequently the earliest evidence of illness. Its intensity varies greatly, corresponding in a measure with the height of the febrile action. At times it is so excruciating as to cause even self-restrained individuals to cry aloud. The face is often flushed,

the carotids visibly pulsating. Restlessness and sleeplessness are common symptoms during this stage. Children, on the contrary, are sometimes drowsy and sleepy. When the temperature is high delirium is prone to supervene. This usually takes the form of talkative incoherence, although some patients become quite violent. Coma is rare in adults, but not uncommon in children. Convulsions are frequently seen in children, more so perhaps in this disease than in any other of the exanthemata. They may be severe and repeated, and may continue even after the appearance of the eruption.

Pain in the back is a symptom so commonly observed that it is believed to be of special diagnostic value. It is not as constant as some of the other symptoms, yet it occurs in more than one-half of the cases. In perhaps one-third of the cases it is sufficiently severe to cause the patient to volunteer information concerning it. Its diagnostic import, therefore, is due rather to its infrequency in the other acute infectious diseases than to its constancy in smallpox. The lumbar and sacral regions are the parts to which the pain is usually referred, although it may extend to the dorsal region. As a rule, it is more severe in unmodified smallpox than in varioloid, yet this rule is subject to many exceptions. In hemorrhagic cases the pain is often of an excruciating violence. Lumbar pain is more constantly seen among female than male patients, owing to the fact that the menstrual function is very liable to be excited by the initial illness of smallpox. In the vast majority of women who are stricken with smallpox the menses appear out of their regular period. This is true of mild as well as severe cases. The premature onset of the menstrual flow occurs with more striking frequency in this disease than in any other of the infectious maladies. Pregnant women are exceedingly liable to suffer from abortion or premature delivery. The pain in the back owing to these causes is given greater prominence in women.

General aches and pains are frequently complained of, appearing at the same time as the headache and backache. These may occur anywhere, but are usually referred to the lower extremities, particularly about the knees. The soreness of the general muscular system may lead to confusion of diagnosis with *la grippe*. *Vertigo*, which is particularly manifest upon the patients assuming the erect position, is a common early symptom. It is often well marked, even in mild cases, for these patients are more apt to rise from their beds. Syncopal attacks may occur in weak individuals.

There is a considerable degree of variation in the character and sequence of the symptoms constituting the initial stage of smallpox. This is shown in the following analysis of 110 cases, occurring in the epidemic of 1901 and 1902: The patients who were taken without selection were closely interrogated as to the nature and chronological development of the various symptoms. The number includes 28 cases of confluent smallpox, 15 with very profuse and semi-confluent eruptions, 29 with eruptions of moderate severity and 29 cases of mild

varioloid. Of this series of 100 patients 22 died. Headache was the most constant of the initial symptoms. The various symptoms mentioned were present in the following percentages: Headache, 86 per cent; chills or chilliness, 78 per cent; backache, 70 per cent; vertigo, 57 per cent; vomiting, 55 per cent; nausea without emesis, 10 per cent.

In some of these cases the symptoms were of marked severity, while in others they were extremely mild. An effort was made to determine the earliest symptom observed by these patients. It is recognized that some inaccuracy must arise from an attempt to chronologically arrange the symptoms from histories thus obtained.

	Cases.
Chilliness or a decided chill was the first symptom in	35
Headache first symptom in	26
Backache first symptom in	16
Vomiting first symptom in	9
General aches and pains first symptom in	7
Vertigo first symptom in	2

In but 2 patients out of the 100 was there complete absence of initial illness; 1 of these was a man, aged twenty-six years, with a very mild varioloid, and the other a colored woman, aged twenty-seven years, with an eruption of moderate severity. Upon close inquiry the latter patient admitted experiencing fatigue upon the day preceding the eruption. It is possible that some negative histories of this character may be due to poor memory or lack of intelligence on the part of the patients.

In the severe cases the initial illness was always well marked, although the classic symptoms were not invariably present. A man, aged fifty-five years, who had a fatal confluent attack had merely as prodromes a severe chill, fever and prostration; headache, backache, vertigo and vomiting were absent. A male patient, aged twenty-nine years, with an eruption of moderate severity, experienced during the initial stage fever, repeated vomiting and pain in the stomach, without any other symptoms. On the other hand, quite a number of patients with very mild eruptions gave a perfect history of the classic initial syndrome. A young woman, aged twenty years, for instance, with only three or four lesions on the face and a few upon the arms and hands, experienced at the onset of the disease headache, backache, repeated vomiting, severe chills, vertigo and aching in the legs.

These observations are in accord with those of most writers, and seem to illustrate the impossibility of forecasting the extent of the eruption from the degree of severity of the initial symptoms. We have frequently seen the most aggravated febrile symptoms followed by a perfectly insignificant eruption. Mild initial manifestations are rarely succeeded by a severe cutaneous outbreak. In general terms it may be stated that severe initial symptoms may be followed either by a profuse or a sparse eruption and that mild initial symptoms are nearly always followed by a mild eruption.

The *urine* in the initial stage is usually more or less diminished, according to the degree of the fever. The solid constituents are not out of their normal proportion, except the chlorides, which are considerably diminished. In severe cases, especially those about to become hemorrhagic, albuminuria may be present. A high grade of fever might be responsible for a small quantity of albumin, but if it be present in great abundance a malignant type of the disease should be suspected. Before giving an unfavorable prognosis, however, care taken to exclude the possibility of preëxisting disease of the kidneys.

The *spleen* may be found enlarged in the initial stage of severe smallpox. In mild cases no enlargement, as a rule, can be detected.

Peculiar *prodromal rashes* often make their appearance during the initial illness. When they develop it is usually upon the second day of the invasive fever. They disappear ordinarily in from twenty-four to forty-eight hours. They may, however, continue several days after the appearance of the eruption. The frequency of these rashes appears to vary in different epidemics. During the widespread and malignant epidemics of 1871 and 1872 they were very common. Osler noted these rashes during this period in 13 per cent of his cases. These eruptions are not so apt to be observed in smallpox hospitals, inasmuch as they disappear commonly before the diagnosis is made and the patient conveyed to the hospital. The most common type is that *resembling measles*, with which disease, indeed, it is liable to be confounded. The eruption has an irregular distribution, being at times generalized and at other times limited to certain regions of the body. It, moreover, differs from the eruption of measles in that the rash is not elevated above the level of the skin and, therefore, scarcely appreciable to the finger when passed over it. Its ephemeral character is also a differentiating feature. This *roseola variolosa*, as it has been designated, has a close analogue in the *roseola vaccinosa* which occasionally appears about the ninth to the eleventh day after vaccination.

The *scarlatiniform* rash is less common that the measles-like eruption. It may involve a large part of the cutaneous surface, but is more apt to affect certain areas, as the thighs, inguinal regions, extensor surfaces of the extremities and the trunk. Some authors refer to the appearance of an urticarial eruption in rare cases.

The *petechial* or *hemorrhagic* initial rash has a special predilection for certain regions of the body which were carefully studied by Simon, of Hamburg. This writer pointed out the frequent occurrence of the eruption in the lower abdominal, inguinal and genital regions and inner aspects of the thighs, constituting a triangle whose base traverses the neighborhood of the umbilicus (the so-called crural triangle of Simon). The "axillary triangle," including the inner aspect of the arm, axilla and pectoral region is also a commonly affected area. The petechial rash is also frequently seen along the lateral surface of the thorax and abdomen. The eruption consists of closely aggregated pin-point to pin-head-sized purplish or clarety spots, which are in such

intimate juxtaposition as to convey the impression of a diffuse redness. Being the result of a hemorrhagic extravasation into the skin, the discoloration does not disappear upon pressure.

Occasionally an erythemato-petechial rash is seen, the eruption partaking of the characters of both the erythematous and hemorrhagic rashes.

The petechial eruptions may occur in cases which later prove to be quite mild. More often, however, they are the harbingers of severe smallpox of the hemorrhagic type. The morbilliform eruptions in our experience are much more common in cases of varioloid, and their occurrence, therefore, may be regarded as an auspicious sign. We are able to recall two cases of smallpox in vaccinated individuals in which the roseolous eruption was practically the only cutaneous manifestation. In one of these cases, it is true, about half a dozen small variolous papules appeared as the initial rash faded away, but they disappeared in two or three days without becoming in the slightest degree vesicular. These cases belong to the class commonly designated *variola sine exanthemate*, which is the most benignant form that smallpox may assume. That such cases are occasionally encountered is evident from the writings of both ancient and modern authors. Perhaps in every epidemic patients are seen who give a history of exposure to smallpox and who, in due course of time, are suddenly seized with chills, followed by headache, fever, vomiting, prostration and pain in the back. These symptoms continue for three or four days, and then subside without the development of any eruption except perhaps one of the prodromal rashes to which reference has been made. It is impossible to explain such cases on any other supposition than that the disease was variola without the eruption. Trousseau refers to cases observed by him in which the only symptoms characteristic of the disease were a "few pustules on the pharynx and the pendulous veil of the palate."

It may be of interest to record the histories of two patients under our observation upon whom but a single variolous lesion appeared:

B. H., aged twenty-six years, suffering from measles, was sent into the Municipal Hospital under the erroneous diagnosis of smallpox. He was immediately vaccinated, but this and subsequent attempts failed. At the end of ten days he was seized with high fever (104° F.), headache and vomiting. A few days later a single papule appeared in the right loin. This went on to vesicle formation, becoming characteristically umbilicated, but dried up within a few days. The patient claimed to have had smallpox at the age of eight years, but showed merely a single pit upon the face.

The following case presents a somewhat similar history:

W. G., a colored lad, aged fifteen years, was vaccinated four years prior to admission; he presented a good vaccination cicatrix. He was brought into the hospital from a house from which several patients with smallpox were removed. On admission he had a temperature of 102° F. and presented other well-marked initial symptoms. On the

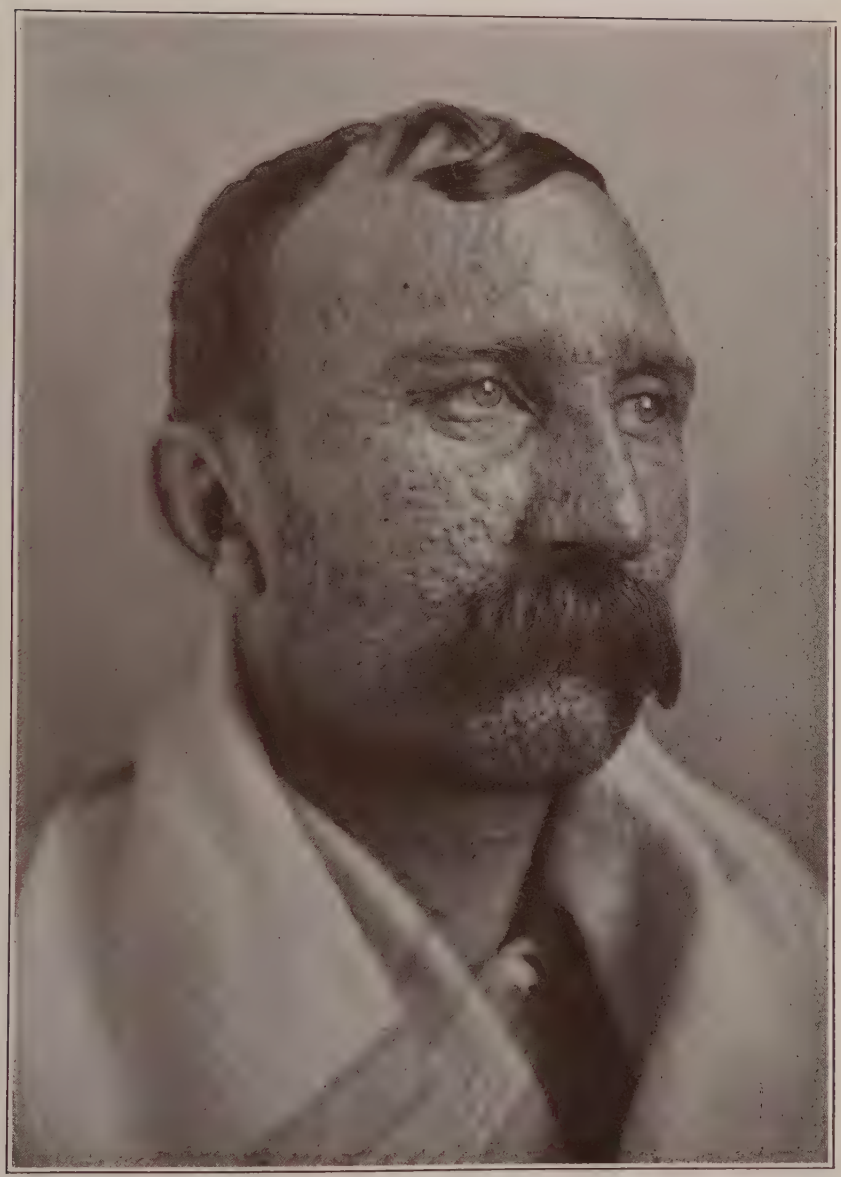
PLATE I

Serial Photographs of Smallpox in an Unvaccinated Man.
Third Day of Eruption.

PLATE II

Fourth Day of Eruption.

PLATE III



Sixth Day of Eruption.

PLATE IV

Eighth Day of Eruption.

PLATE V

Tenth Day of Eruption.

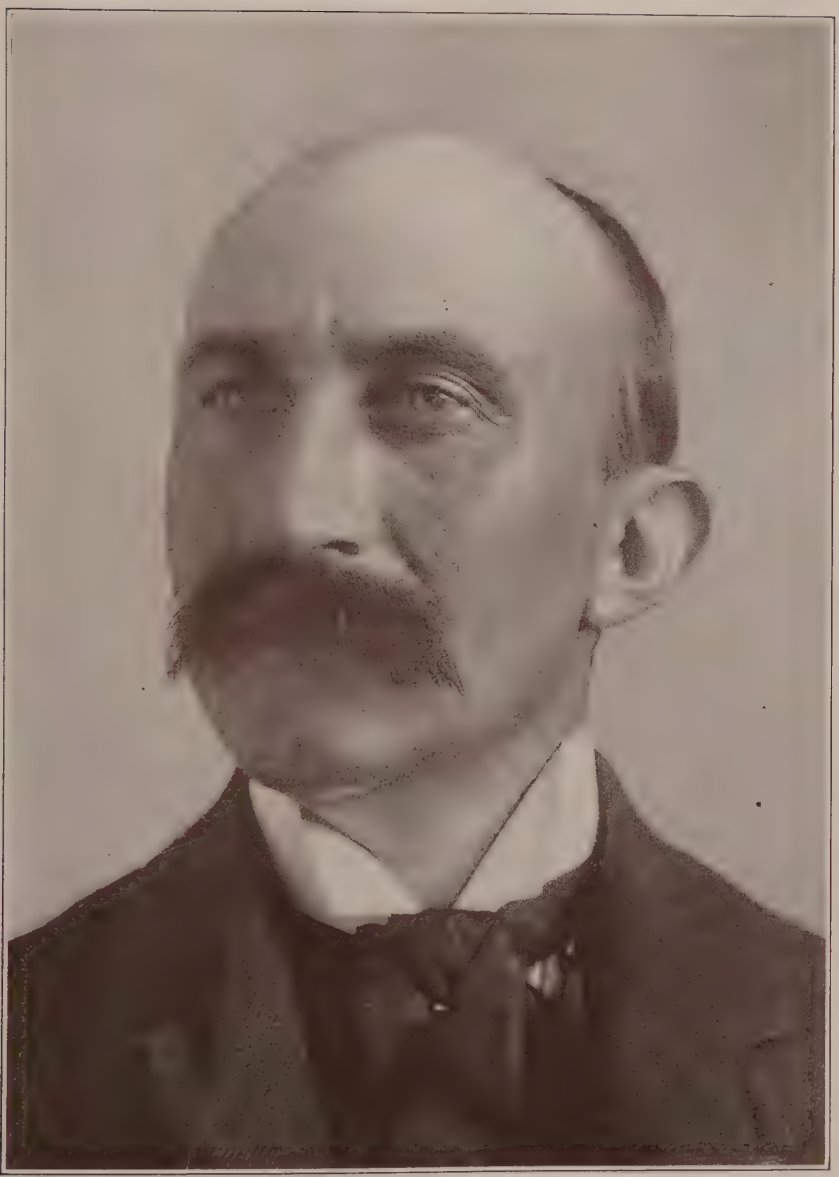
PLATE VI

Twelfth Day of Eruption.

PLATE VII

Sixteenth Day of Eruption.

PLATE VIII



After Recovery. Scarring present, but not deep.

subsidence of these symptoms he developed a single typical papule on the trunk.

These cases come almost within the definition of variola without an exanthem. If smallpox may occur with the appearance of but one lesion, there is no reason why it should not at times develop without any eruption whatsoever.

The duration of the initial stage is commonly forty-eight to seventy-two hours; it is rarely less, but it may be somewhat prolonged. Trousseau held that the longer the eruption was delayed in its appearance, the more favorable was the prognosis. This is scarcely borne out by experience. It is misleading to draw any prognostic conclusions from the duration of this stage.

It is commonly stated in text-books that upon the appearance of the eruption of smallpox the fever subsides and a general abatement of the systemic symptoms occurs. In our experience a decided remission in the temperature does not take place in unmodified smallpox until second, third or fourth day of the eruption. In very mild cases, more particularly in those modified by previous vaccination, the temperature may fall to normal as the exanthem makes its appearance. With the fall of the fever there is a cessation of the pains and a general improvement in the condition of the patient. In mild cases of varioloid the illness of the patient is terminated at this stage. In severe cases the improvement constitutes but a brief respite, and then the grim struggle with the disease begins.

Stage of Eruption.—By carefully observing the early stage of the disease it will be found that the true eruption makes its appearance with remarkable regularity on the third day of the illness, calculating from the day on which the initial chill or rigor occurred. In modified smallpox deviations from this rule may be noted. The eruption almost always appears first on the forehead and temples near the edge of the hair and on the wrists. Not infrequently it is seen first on the upper lip and around the mouth. It rapidly spreads to the scalp, face, neck, ears, forearms and hands, always showing a decided preference for the cutaneous surfaces habitually exposed to the atmosphere. In the course of twenty-four hours, sometimes somewhat earlier, it extends to the body and lower extremities. It does not simultaneously affect these regions, but attacks in succession the back, arms, breast and finally the legs and feet. In rare cases the exanthem may be first noted on the trunk or extremities.

The full complement of lesions does not make its appearance at once in any given part; the eruption continues rather to multiply for two or three days before its definite limit is reached. In varioloid new lesions may continue to appear for a longer period of time. Upon carefully examining the eruption it is seen that many lesions develop at the sites of hair follicles or orifices of the sebaceous and sudorific glands.

The eruption begins as small red spots or *macules*, some of which

may be so small and faint as to be scarcely visible, while others reach the size of a lentil seed. The color is at first pinkish-red, later assuming a deeper tint. In many cases the lesions on the trunk and extremities present the appearance of flea bites. The lesions gradually increase in size and number, becoming more and more prominent, so that in twenty-four hours they assume the form of elevated *papules*, with a characteristic feel. The early papules, particularly about the forehead and cheeks, may be more demonstrable to the sense of touch than to the eye. They possess a peculiar induration, and convey to the finger a sensation similar to that which would be produced by grains of shot embedded in the skin. The "shotty" feel varies in degree in different cases. Some papules are extremely hard, while others possess comparatively little induration. They are at first always discrete, but they may rapidly increase in number and become confluent, even before the vesicular stage is reached.

On the third day of the eruption, or the fifth day of the disease, very many of the lesions which made their appearance first will be found to contain a little clear serum. Indeed, in many patients one will be able to note on the second day a lesion here and there which has become vesicular in advance of the general eruption. These precocious vesicles are frequently of diagnostic import, enabling one in doubtful cases to assert the variolous nature of the disease. By the fourth or fifth day all of the lesions are converted into *vesicles*. At this stage they commonly have the size and shape of a split pea. Small vesicles are apt to be conical or acuminate, while the larger lesions have a convexly flat or hemispherical appearance. The vesicle of smallpox is extremely firm; not infrequently it feels harder to the finger than the papule from which it developed. In no other disease do the vesicles acquire such a degree of induration and hardness. The color of the vesicle is at first pinkish, the tint extending to the areola surrounding it. Later, as the fluid exudation into it increases, it assumes a peculiar opaline or pearly hue. This, with the shining and glistening surface, imparts to the vesicle a most distinctive appearance. One of the most characteristic features of the smallpox vesicle is the so-called "umbilication." In the smaller acuminate vesicles this is seen as a minute central depression or invagination, representing in all probability the mouth of a hair follicle or sweat duct. This form of umbilication may occasionally be met with in other cutaneous diseases, when the lesions are situated at the mouths of the pilary or sudoriparous orifices. In the larger pea-sized vesicles the umbilication is seen as a round, oval, or slightly irregular indentation. In this case the depression is flatter and is probably due to the bulging of the periphery of the pock. This latter form of umbilication is of important diagnostic value, as but few other vesicular diseases produce quite the same appearance. The forearms and the backs of the hands are, perhaps, the regions upon which umbilication is most characteristically seen. Umbilication is

only observed in a certain proportion of vesicles. It is by no means a constant feature of smallpox eruption and, indeed, is not infrequently absent altogether. This is particularly true of cases of varioloid. A form of secondary umbilication is commonly seen during the stage of decline or desiccation, when the pustules, as the result of rupture or drying, show a depression in the center.

If one observes closely the large, clear vesicles of about the fifth or sixth day, particularly those situated on the dorsal surfaces of the hands, one can frequently discern through the epidermal roof something of the interior construction of the lesions. They will be seen to be made up of compartments which are divided by vertical septa, very much like the divisions of an orange. The vertical partitions are formed by the spinning out and reticulation of the epithelial cells of the rete mucosum. This accounts for the multilocular character of the smallpox vesicle, and explains the inability to completely evacuate its contents by a single puncture. Large, fully developed vesicles frequently show at their central summit a disk of the color of yellowish

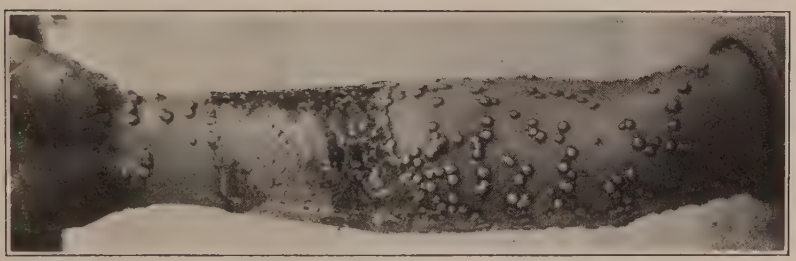


FIG. 35.—Smallpox eruption showing confluence over an area upon which iodine had been applied before the eruption appeared.

serum, and around the periphery a whitish, puriform ring looking not unlike an *arcus senilis*.

The predominance of the eruption of smallpox on the face and terminal extremities is to be accounted for by the greater vascularity of the skin in these regions. That lesions are attracted by an overfilling of the cutaneous vessels is seen in the excessive development of the eruption wherever the skin has been irritated or congested. It is a common experience in the hospital to see in a discrete case of smallpox a profusion of lesions over a rectangular area in the lumbar or epigastric region where a mustard plaster had been applied during the initial stage for the relief of pain. Fig. 35 shows a marked confluence of the pustules in the form of a band on the wrist where the patient had applied iodine for a sprain received before his illness.

It is only when mechanical or chemical irritation is applied to the skin before the appearance of the eruption that an increase in the number of lesions is produced. We have frequently applied tincture of

iodine and similar applications to the skin in the early days of the eruption without augmenting the variolous crop in the region thus treated. Some of the older physicians purposely irritated the skin of certain portions of the body with the hope of deflecting the eruption from the face to the regions thus treated. Unfortunately, the eruption was increased in the manipulated areas without diminishing the number of lesions on the face.

FIG. 36.—Smallpox in an unvaccinated colored man, semi-confluent on face, discrete on body and extremities.

Stage of Suppuration.—The contents of the vesicles gradually become more and more turbid, as the result of the increased exudation of leukocytes, until the lesions become frankly purulent. This condition is usually reached in unmodified smallpox about the sixth day of the eruption, and marks the beginning of the stage of suppuration. The pustules now, in good part, become large and globular, and stand out prominently from the skin. Their color varies somewhat in different

PLATE IX

Well-pronounced Discrete Smallpox in an Unvaccinated Subject on the Eighth Day of Eruption, Showing the Relative Sparsity of the Lesions Upon the Trunk.

cases. At times the pustules acquire a distinctly yellowish tint not unlike the color of ordinary pus. Frequently they retain until ruptured a peculiar chalky or grayish-white hue. The reddish areola, which is observed about the vesicles, develops in this stage into a broader, deeper-hued, violaceous halo. Where the lesions are closely aggregated the entire interpustular integument becomes reddened and tumefied.

On the face and scalp, where the eruption is apt to be profuse, the redness and intumescence are so extreme as to render the features of the patients completely unrecognizable. The eyelids, as the result of edema of the loose areolar tissue, become enormously puffed and completely close the palpebral cleft, which is bathed in a puriform secretion. The patient for a time is unable to see, owing to a complete closure of the eyelids. The lips, nose and ears are distorted, the normal contour

FIG. 37.—Discrete smallpox eruption on the ninth day, showing marked edema of the face, completely closing the eyelids.

of the face is lost and the entire head swollen beyond human proportions. The patient presents a most revolting and loathsome appearance. One seeing the disease for the first time in this stage is apt to be appalled by the horrible spectacle. The patient is sorely distressed by the inflammation and swelling of the scalp, inasmuch as contact with the pillow is a source of unendurable pain.

As the eruption on the body and lower extremities is later in making its appearance than that on the face, so also is it later in reaching maturation. When the lesions upon the face have become vesicular it will be found that the efflorescence upon the trunk and extremities is still in the papular stage. In like manner the facial lesions will have advanced to pustulation by the time that the eruption on the body has become vesicular. There is noticeable, therefore, this regular multiformity in the character of the lesions upon the different portions of the body. About the eighth day the pustules on the face have

reached their greatest development, and the process of retrogression then begins. They become yellowish, present a shrunken or shrivelled appearance, and rupture or collapse. On rupturing the pustules give exit to a viscid, glairy, dirty-yellow pus, which dries in the form of yellowish or brownish crusts. A gradual subsidence in the inflammation and swelling takes place, and the normal outlines of the face are once more restored.

During the stage of pustulation the lesions which exhibited umbilication become distended and globular, thus effacing the central depression. The epithelial bands holding down the center of the lesion in all probability become dissolved away, permitting the roof of the pustule to assume a hemispherical form.

The eruption on the trunk is almost always much less abundant than on other parts of the body. Not infrequently the hypogastrium is quite free from pustules, even when the face and hands show a marked degree of confluence. Exceptions to this rule are, however, occasionally met with. We have seen patients the skin of whose body was so profusely covered that it would have been impossible to place the tip of the finger upon a healthy area of skin. Of course, in such cases the danger to the patient is correspondingly increased, inasmuch as the gravity of the disease is, as a rule, directly proportionate to the extent of the eruption.

In a well-pronounced case of semi-confluent smallpox under our care an approximate count of the number of lesions was made. This was accomplished by dividing the cutaneous surface into certain areas by means of a colored crayon and counting the pustules within these boundaries. Upon the face and scalp the confluence of the pustules precluded the possibility of their being counted. A conservative estimate of the number present was therefore made.

The number of lesions computed upon the different portions of the body is herewith appended:

Fingers on one hand:	
Thumb	61
Index finger	97
Middle finger	95
Ring finger	81
Little finger	58
Total fingers on one hand	392
Dor al surface of one hand	382
Palmar surface of one hand	129
Total lesion on both hands	1,806
Forearms	4,400
Arms	2,840
Chest	1,000
Abdomen	175
Thighs	4,180
Legs	2,850
Feet	750
Back	5,700
Estimated number on face and scalp	3,000
Total	26,701

By evacuating some of the pustules with a pipette we estimated that the lesions at the height of their development each contained about 3 drops of pus. Such a computation developed the surprising fact that the patient referred to carried in his skin about 5 quarts of pus.

We have seen large men with more profuse eruptions, who must have had in the neighborhood of 40,000 pustules. With this prodigious amount of purulent material in the skin the wonder is that any patient thus afflicted should recover.

The pustules on the trunk appear to have a more superficial seat in the skin than on cutaneous surfaces constantly exposed to the air; hence they are not accompanied by the same amount of inflammatory swelling or ulcerative destruction of the cutis. There is, moreover,

FIG. 38.—Severe smallpox in a patient who had had during his life seven *unsuccessful* vaccinations.

very little tendency on the trunk and lower extremities to confluence of the lesions. We frequently note a coalescence of two or three pustules as a result of their contiguity, but the vast majority of the lesions remain discrete.

This statement, however, does not apply to the efflorescence *on the hands and feet.* In these regions the degree of confluence may be intense and cause the patient great suffering. As a result of the thickness of the overlying epidermis on the palms and soles, the pustules do not acquire as great a prominence as elsewhere. Being bound down by the tense and unyielding horny layer of skin, pressure is made upon the delicate underlying cutaneous nerves, producing distressing pain. In a severe attack of smallpox the palms and soles, the fingers and toes and the dorsal surfaces of the hands and feet are profusely covered. When

the pustular stage is reached the patient becomes perfectly helpless; he is unable to feed himself or in any way utilize his hands. It is pitiful to behold him in bed, with his hands and fingers semi-flexed and his arm outstretched for fear of the dreaded contact with the bed-clothing. At times the pustules on the back of the hands fuse and produce large bullæ, or even an extensive undermining of the epidermis similar to that seen in a bad scald.

During the suppurative stage a most penetrating and offensive odor emanates from the body of the patient, and from the pus-stained bed and body linen. This stench results from the decomposition of the effete and purulent discharge, and is not peculiar to smallpox. In

FIG. 39.—Well-pronounced smallpox on the eighth day, occurring during a particularly mild epidemic, the lesions being very superficial.

neglected cases the odor is most sickening, and may pervade the atmosphere of a room or, indeed, of an entire house.

Eruption Upon the Mucous Membranes.—Simultaneous with the appearance of the smallpox efflorescence upon the cutaneous surface, or a little earlier, the eruption develops upon the adjacent mucous membranes. The involvement is almost exclusively confined to those mucous surfaces which are near the external orifices, or to which the air has access. The eruption early attacks the lining of the mouth, nose and pharynx, and in severe cases the larynx, bronchi and esophagus. The extent of the enanthem bears a direct relation to the severity of the eruption of the skin. The lesions, however, are seldom as profuse upon the mucous surfaces as upon the integument. If an exami-

nation of the mouth and fauces be made at the very beginning of the eruptive stage, small yet distinct red spots may be seen upon the roof of the mouth, buccal surfaces and anterior arches of the palate.

These macules are pin-head-sized and larger, and of an intense red color, which contrasts with the violaceous or bluish-red tint of the surrounding mucous membrane. In a short time the spots become slightly elevated or papular, frequently exhibiting a whitish, glistening center. The parallelism with the evolution of the cutaneous pock ceases at this stage of the development. The mucous membrane lesion does not pass through the stage of papule, vesicle and pustule, but pursues a characteristic course which is determined by its peculiar structure and its different environment. There is perhaps an effort on the part of Nature toward the formation of vesicles, but the thin and delicate epithelium which serves as a covering is destroyed by the macerating influence of the moist secretion in which they are constantly bathed. As the eruption upon the skin becomes vesicular and pustular, the lesions in the mouth assume a whitish or grayish appearance, with but little, if any, elevation above the surface. The denudation of the epithelial covering of the pocks leads to the production of circumscribed erosions or superficial ulcerations.

Soreness of the throat, particularly on swallowing, is one of the most distressing symptoms of the early eruptive stage. But few patients with well-marked attacks escape this suffering. Even when the patient is feeling otherwise well the condition of the throat constitutes a source of bitter complaint. In severe cases, at a later stage, the mucous membrane of the mouth is so abraded, swollen and painful that the use of solid food is rendered impossible, and the patient is forced to subsist entirely on a liquid diet.

The tongue is often the seat of lesions which seriously embarrass its movement in speaking and eating. Occasionally an intense form of glossitis is set up, causing the organ to swell so enormously as to prevent its retention wholly within the mouth. This condition, which was designated by the older writers as *glossitis variolosa,* is apt to greatly interfere with swallowing and is under all circumstances to be regarded as an unfavorable sign.

Much annoyance is occasioned by the presence of the eruption in the nasal cavities. The mucous membrane is at first swollen and inflamed and later covered with crusts which obstruct the nares and render nasal breathing difficult and often impossible. This is particularly a source of distress to nursing infants, who are obliged to release the nipple from time to time to obtain the necessary amount of air.

The eruptive process may involve both the pharynx and larynx and cause so much inflammation and swelling as to make deglutition difficult or impossible, or it may lead to the production of hoarseness and complete aphonia. In severe cases an acute edema of the glottis may develop, which may seriously or even fatally impede respiration. Trousseau records several fatal cases of this character: "Three small-

pox patients, on the eighth day of the disease, which had run a perfectly normal course, were suddenly seized with a fit of suffocation which carried them off in a few seconds, before there was time for anyone to come to their assistance. In one patient autopsy showed laryngitis, with variolous lesions below the glottis."

In severe smallpox in children we have found it necessary in 4 instances to employ intubation in order to prevent asphyxia. In all of these cases there was laryngitis with considerable swelling of the mucous membrane. Although relief was temporarily afforded, death ultimately occurred in all 4 cases. In one of the children the laryngeal stenosis came on late after complete decrustation had occurred on the skin, and at a time when the child appeared to be on the road to recovery.

The mucous membranes of the lower portion of the body may also be involved. The eruption may attack the vulva and the mucous surfaces of the vagina, but the lesions in these parts are not apt to be abundant. The lower part of the rectal mucosa may also be the seat of the variolous eruption. The meatus urinarius is occasionally involved in both males and females, but the urethral channel nearly always escapes.

Delirium.—As previously stated, a variable degree of delirium may accompany the high fever of the initial stage. In our experience the most violent disturbance of cerebration occurs during the early eruptive period. This may be, in some cases, merely the continuation of the earlier delirium, but in others it seems to begin after the exanthem has made its appearance. Some patients are apparently the subjects of delusions of persecution and of hallucinations, and imagine that some one is about to do them bodily harm. Acting on this supposition, the demented patient attempts to escape from the hospital and, what is quite strange, will amost always prefer to gain egress through the window. On a number of occasions patients, by the exercise of cunning and the awaiting of a favorable opportunity, have effected their flight with marvellous celerity, and have gained a temporary liberty in this manner. In some patients the temporary derangement takes the form of a suicidal or homicidal mania. One of our patients attempted self-destruction by striking himself on the head with a drinking mug, inflicting several large and painful wounds.

On another occasion a female, by cunningly embracing an opportune moment, quickly ran to an open fire-grate, on which she seated herself. While her clothing was burning around her and her flesh charring she violently resisted the efforts of the nurse to extricate her. We recall another patient who rose from his bed at night, struck the nurse to the floor and effected his escape in his night-clothes; he wandered a considerable distance from the hospital, and succeeded, by a shrewd and plausible story, in prevailing upon the credulity of a wagon driver, who conveyed him to his desired destination.

These patients are often able to answer questions coherently, and one, unprepared, may be completely deceived as to their mental

condition. They are apt to exhibit, however, some injection of the conjunctivæ and a wild expression of the countenance. This form of delirium was called by the older writers *delirium ferox*.

Patients thus affected require to be closely watched, and, if necessary, restrained in bed by straps or other means. When a patient complains of persecution or asks to be permitted to attend to some business at home for a day or two close surveillance is necessary.

We have observed this active delirium most often during the papular and vesicular stage of the eruption. When it occurs it is usually associated with the confluent variety of smallpox, yet we have known it to occur in comparatively mild forms of the disease or when the patient had become quite apyretic. The persistence of the delirium for a number of days is a symptom of evil portent.

The delirium which is seen later, during the decline of the eruption, is of a different character. It is then of a low, muttering form, and frequently associated with general tremor, dry tongue, quick and tremulous pulse and a collapsed appearance of the features. These nervous symptoms are not peculiar to smallpox, but may be seen in the terminal stage of typhoid and other fevers.

The various forms of delirium, while more frequently observed in alcoholics, appear to be the result of the poison of the disease acting upon the nerve centers.

It has already been stated that the initial *fever* in unmodified smallpox continues high until the third or fourth day of the eruption, when there occurs either a well-marked remission or a brief period of apyrexia. In very mild cases the fever subsides earlier. The fall of the temperature at this stage, even in severe cases, is not infrequently very rapid, so rapid, indeed, as to drop from a high degree to normal or even subnormal in the course of twelve or eighteen hours. The difference between the morning and evening temperature is not great, although the latter, as a rule, is slightly higher. When the temperature falls there is usually amelioration of all the symptoms. The pulse becomes almost normal; the respirations are easier; the pain in the back, headache and irritability of the stomach all disappear, except in critical cases; the delirium ceases, enabling the patient to rest and enjoy refreshing slumber. Even the appetite may return, and the patient may be led to believe that the critical period of the disease has passed and that recovery has begun. The subsidence of the symptoms is never so complete in *variola vera* as it is in varioloid. In the latter variety the fever and other systemic symptoms frequently disappear, and the beginning of convalescence is established; but in the former the chief danger is yet to be encountered.

At or shortly after the commencement of the stage of suppuration the temperature again begins to rise, and continues elevated until the completion of the eruptive process, or longer if complications arise. This rise constitutes the so-called *secondary or suppurative fever* of smallpox. This latter pyrexia is not apt to equal in intensity the ini-

tial elevation of temperature. When the disease is of moderate severity the temperature may not rise above 102° or 103° F., but in well-marked confluent cases it frequently reaches 104° F., rarely exceeding that point. When hyperpyrexia develops, the thermometer registering 105°, 106° or 107° F., the danger of a fatal outcome is correspondingly increased. The maximum degree of fever is often reached during the hours which immediately precede dissolution. Wunderlich reports an an antemortem temperature of 109.2° F and Simon has seen temperatures of 110° and 112° F. immediately after death.

The secondary fever commences ordinarily on the fifth or sixth day of the eruption, when the vesicles begin to fill with pus. It is of indefinite duration, depending directly upon the extent and severity of the cutaneous outbreak. In a well-marked discrete or semi-confluent smallpox the pyrexia is apt to last from three to six days. In severe confluent cases it may continue for eight to twelve days or longer. It is not uncommon for the secondary fever to merge without intermission into the pyrexia produced by the common septic complications, such as boils, abscesses, etc. The elevation of temperature may, under such conditions, continue for four, five, or six weeks or even longer. In the beginning of the suppurative fever the variation between the morning and evening temperature is apt to equal 1° or 2° F. The maximal elevation usually occurs, in severe cases between the seventh and tenth days. Later, when boils and abscesses develop the diurnal variations are most pronounced, the evening fever not infrequently reaching 104° or 105° F., while the matinal temperature registers only 99° F. The pulse and respiration correspond in a general way with the temperature curve. The pulse, however, is apt to be higher in proportion to the temperature than during the initial stage. With a temperature of 104° or 105° F. the cardiac pulsations not infrequently reach 140 or 150 to the minute. When the morning remission occurs there is a considerable slowing in the pulse-rate. As is quite to be expected, the patient experiences more comfort in the mornings than later in the day. During the pustular stage the chief complaint of the patient is the general soreness of the skin. The couch upon which he lies is metaphorically, if not actually, "a bed of thorns;" whichever way he turns he makes pressure upon the sensitive and inflamed pocks. Nervous apprehension, restlessness and sleeplessness are prominent symptoms of this period. The patient is conscious of an increasing degree of prostration, and is frequently much concerned as to the outcome of the illness. It becomes necessary to allay the nervousness of the patient and induce sleep by the administration of an anodyne. At the end of the eighth or ninth day a sudden improvement in the general condition of the patient is often observed. The sufferer becomes brighter, volunteers information that he feels better, and exhibits altogether a lesser degree of prostration. This is usually coincident with the onset of the period of involution and retrogression of the eruption.

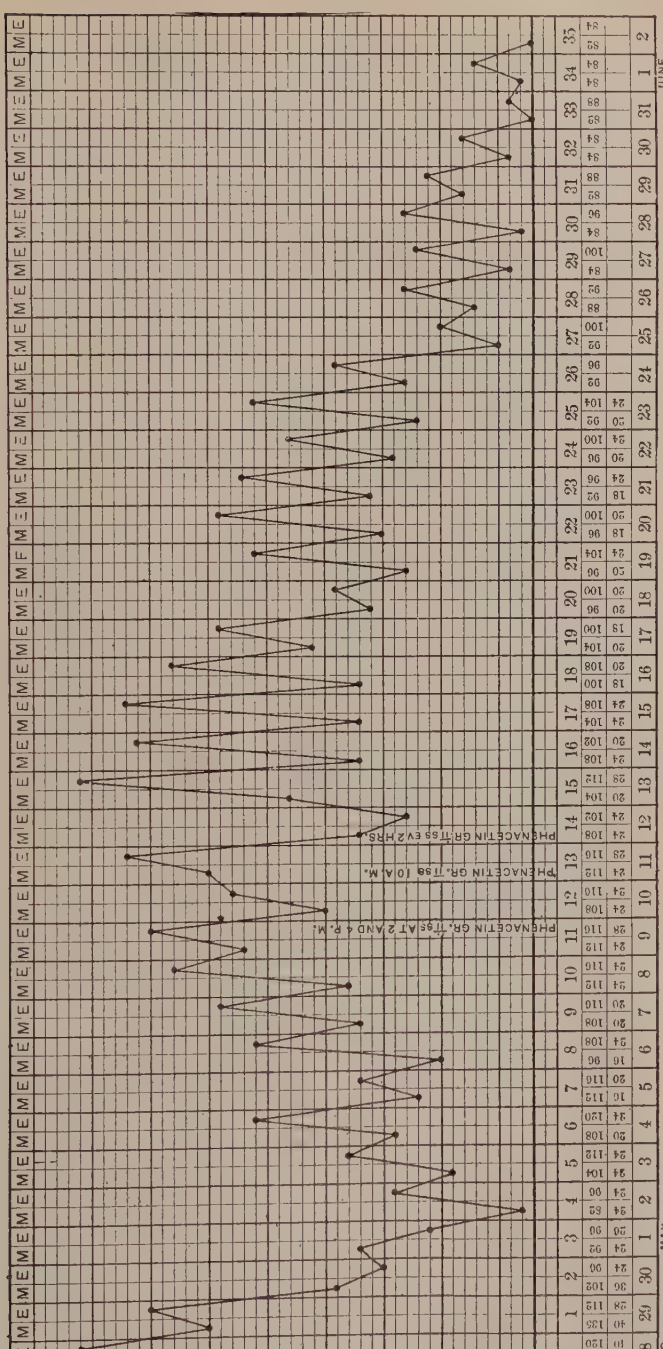


FIG. 40.—Temperature record of confluent smallpox.

Period of Involution and Retrogression of the Eruption.—The exanthem of smallpox reaches the acme of its development with the completion of the pustular stage. This constitutes the turning point not only of the eruption, but frequently of the disease. The first evidence of retrogression of the exanthem is noted in the subsidence of the inflammatory swelling of the skin, more particularly in the

FIG. 41.—Smallpox in the late pustular and desiccative stage. Arms and hands show secondary umbilication due to rupture and central collapse of pustules.

immediate neighborhood of the pustules. The abatement is first seen on the face, where the redness and edema have been most conspicuous. The eyelids become less swollen, permitting the patient to again perceive the grateful light of day. The tumefied features gradually assume their normal contour, and the patient begins to acquire some semblance of his former self. Synchronous with the disappearance of the intumescence the pustules begin to dry; this period is called, there-

fore, the *stage of desiccation*. The drying of the contents of the pustule is soon followed by a casting-off of the crusts, when the *stage of decrustation* is entered upon. Nature in this manner attempts to rid the surface of the skin of the effete products which have there collected and finally restore it to its normal condition.

The involution of the smallpox exanthem does not occur simultaneously upon all portions of the body surface, but follows the same sequence observed during the development of the eruption. It is but natural, therefore, that the first evidence of desiccation should be found in the facial lesions. The pustules in this region may dry without rupture, although more commonly the purulent contents of the lesions exude upon the surface and dry in the form of yellowish crusts. This color gradually becomes darker until it assumes a brownish tint. In neglected cases the crusts may become almost black, enveloping the face in an unsightly, immovable mask. The adherence of the crusts to the subjacent tissues varies in degree according to the depth and

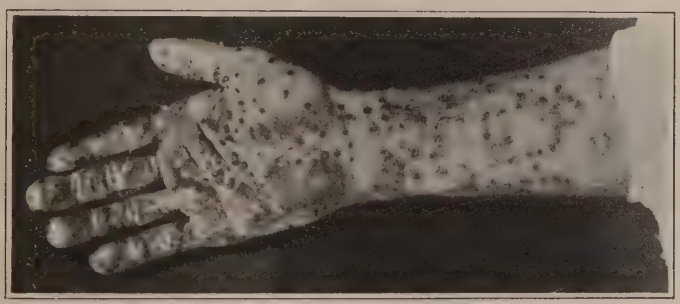


FIG. 42.—Drying of pocks on palms.

intensity of the involvement of the cutis. Where the pustule is superficially seated and there is no ulceration of the skin, the crust is readily detached, exposing to view merely a reddened area of the skin.

At the same time that desiccation is well established on the face, the trunk and extremities will exhibit lesions distended with fluid pus. These rupture, form crusts and then pass through the process just described. At this period of the disease the offensive odor previously mentioned becomes most marked; in some cases it is quite unbearable, especially when the contents of the pustules discharge and decompose on the skin or soak into the bed-clothes and there undergo putrefaction.

After the rupture of large pustules the centers frequently dry and sink in, producing a cup-shaped depression or umbilication. This *secondary umbilication* differs from the primary variety in being distinctly larger, more conspicuous and occurring at a much later stage of the eruption. This form of umbilication is most typically seen on the dorsal surfaces of the hands.

When the variolous pocks desiccate without rupture they undergo

a gradual condensation of structure and a deepening of their color. When they are completely dried they are convexly flat, rounded, of horny hardness and of a characteristic reddish-brown or mahogany color. Upon the back of the hands the dried, horny pock not infrequently preserves in its center a well-marked umbilication. Some of the crusts exhibit peculiar markings resembling an x or a maltese cross. In severe smallpox these horny pocks are usually limited to the hands and feet. In varioloid they may develop in other regions also, even upon the face. In this case the pustule, which is usually small, contracts into a hard, horny, shining crust of a reddish-brown color. These crusts are often of diagnostic value, particularly when mild cases are seen at a late stage of the disease.

FIG. 43.—Dried pocks embedded in the horny layer of the palms of the hands.

Upon the palmar and plantar surfaces the smallpox lesion dries into the mahogany-colored crust described. These pocks have the shape of lentil seeds, and are embedded in the thick, corneous layer of the epidermis. Here they remain for weeks if undisturbed, becoming denser in structure and darker in color. But few patients have the patience to wait for the spontaneous shedding of these crusts. It is a favorite occupation of convalescents to shell out the dried pocks from their epidermal beds. Inasmuch as the pocks in this region usually have their seat in the epidermis, nothing is left save small excavations in the horny layer. The uppermost layer of the epidermis is later removed through the process of desquamation. The mahogany-colored pocks upon the palms and soles present a quite characteristic appearance, which may render aid in the diagnosis in doubtful cases. In very

mild cases minute pocks not larger than pin-heads are found interspersed with the larger lesions.

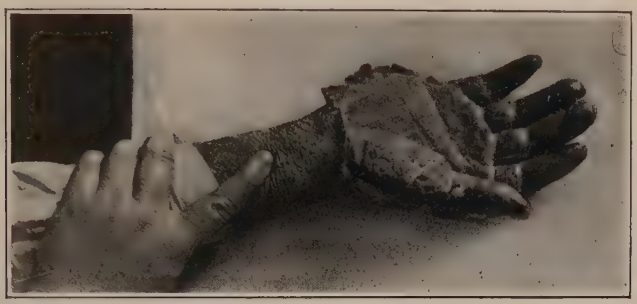


FIG. 44.—Exfoliation of the palmar epidermis containing embedded pocks occurring in the later stage of severe smallpox.

FIG. 45.—Soles of feet from which the hard, embedded pocks have been removed.

The stage of desiccation usually begins about the eleventh or twelfth day of eruption; in mild cases it commences earlier, while in grave forms of the disease it is postponed. If the case is to end in recovery there is at this time not only improvement in the cutaneous symptoms,

but also an amelioration in the general condition of the patient. With the involution of the exanthem, the fever subsides and the pulse lessens in frequency. In favorable cases the temperature each day more nearly approaches the normal standard. If there be considerable involvement of the skin and mucous membranes the temperature falls less rapidly, or if complications arise it continues for a varying period according to the nature of the associated conditions. Although the fever is steadily decreasing, the patient is still in danger from exhaustion, for the heart, kidneys and other organs have been severely taxed by the septicemic poisoning.

The mucous membrane lesions of the upper air passages improve in favorable cases at a rather earlier period than the cutaneous manifestations. The distressing pain on swallowing has often disappeared by the sixth day. The nasal, buccal and pharyngeal eruption, being less deep and destructive, undergoes a comparatively rapid involution.

In regular cases of *variola vera* it usually requires, after desiccation has commenced, from three to four weeks for all of the crusts to become detached and fall off. This makes the entire duration of the disease about five or six weeks.

During the drying stage a new symptom is added to the sufferer's already extensive category of ills. The incrustation of the pustules is accompanied by the development of *itching*, which varies in intensity from slight annoyance to unendurable distress. Adults are usually enabled to restrain themselves from scratching by the exercise of self-control. Children, on the other hand, yield to the impulse to purchase relief by scratching or rubbing, with the result that injury is often inflicted upon the skin. It is not uncommon to see in children, who have had unbridled license in the use of their hands, large, abraded, bleeding surfaces or crusted sores where the pustules have been gouged with the finger-nails. It is popularly believed that the scarring in smallpox is due to secondary injury from scratching. While this agency may be a factor in the production of a few of the cicatrices, the vast majority of them result from the destruction of portions of the corium by the variolous inflammation. That finger traumatism plays but an inconsiderable role in the scarring is evidenced by the fact that children, despite the mechanical violence which they inflict upon the skin, escape as a rule with less disfigurement than adults. This is doubtless due to the fact that the pocks in children are more superficially situated in the integument. The most serious consequence of scratching is in the increased liability to pyogenic infections of the skin and the subcutaneous tissue.

It is only after the completion of the decrustation that one can determine the extent of permanent injury to the skin. If the crusts have been softened off by unguentous substances or mechanically removed, small, irregular depressions filled with granulating tissue show where the integrity of the papillary layer of the skin has been affected. On the spontaneous shedding of the crusts these areas will be seen as red-

dish, cicatrized excavations. The extent of scarring depends entirely upon the depth to which the destructive inflammation has extended. Pocks which remain encapsuled within the epidermis will leave no permanent evidence of their presence. They will be followed by reddish stains, the result of a passive hyperemia of the papillary bloodvessels. These discolorations are quite disfiguring in themselves, but disappear in the course of a few months. On exposure to cold the reddish stains acquire a bluish or purplish appearance. As time goes on the reddish color becomes darker and eventuates in a brownish *pigmentation*. This pigmentation is fortunately less conspicuous and less persistent on the face than on the covered surfaces. Even after several months the trunk and limbs frequently exhibit stains of a *cafe-au-lait* hue. In persons of swarthy complexion and in negroes the pigmentation is greater than in fairer-skinned individuals. The stains in the African race are often quite black and appear to persist longer on the face than in Caucasians. Where the true skin has been destroyed in negroes the normal pigment of the skin is frequently lost. In such cases a whitish or pinkish discoloration is seen in the center of the scar, with a hyperpigmented zone surrounding it.

After the lapse of three or four months the *scars* of smallpox assume a whitish color, paler, indeed, than the surrounding integument. They may be round, oval, linear, stellate, radiate or irregular, according to the configuration or grouping of the lesions which caused them. They may be large or small, deep or shallow; not infrequently they present sharp, overhanging edges. Indeed, there is nothing specially characteristic about the pits left after variola, save their extent and distribution. Affecting most profusely and conspicuously the face, they give rise to the well-known "pock-marked" countenance. It is well to remember, however, that similar pits sometimes follow a severe acne, particularly of the necrotic type. The writers have seen scarred acne patients who might have passed for variola subjects. The older writers gave to acne the significant title of "stone pock."

By a curious irony of fate, Nature obliterates the remains of the vast majority of variolous lesions upon the covered surfaces of the body, whereas indelible evidence is left upon the face and frequently the hands to bear witness to the cruel disease through which the patient has passed. Time, however, accomplishes much toward the effacement of the more superficial scars and the mitigation of the disfigurement produced by the deeper cicatrices.

The hair of the head, beard, eyebrows, etc., may be lost after the termination of a severe smallpox, especially in cases in which the eruption has been profuse in these areas. This *alopecia* is probably in part of febrile origin and partly the result of the local influence of the exanthem. Restoration of the hair usually occurs, and this is complete except in areas in which the hair papillæ have been destroyed by the variolous lesions.

The *nails* of the fingers and the toes may be shed in severe cases.

This is usually accomplished slowly through the pushing off of the old nail by the new one growing from behind. After six or eight weeks a sharp, elevated ridge is seen near the nail fold; this represents the free border of the new nail, which in the course of time extends forward. Not infrequently variolous lesions are located beneath the nail. These *subungual pocks* are of a purplish or reddish-brown color, looking not unlike traumatic ecchymoses.

FIG. 46.—Deep scarring and temporary loss of hair after recovery from confluent smallpox.

When convalescence sets in in uncomplicated cases improvement in the general condition of the patient is rapid. The appetite returns and is apt to become keen, sometimes even voracious. The digestive functions are active and the patient rapidly regains strength and weight.

Impetigo Variolosa.—During the period of desiccation and incrustation in smallpox certain secondary changes commonly occur upon the skin. One of these is the development of sparsely distributed blebs containing a thin, dirty-yellow fluid. These may originate in several distinct ways. They may spring up upon previously healthy interpustular areas of skin, or they may result from a direct conversion of the pustules into blebs. At times a pustule is seen, one-half of which is still yellowish, while the other half is spreading out into a muddy-colored bleb. The blebs are commonly flat, although at times they rise prominently from the surface; they vary in size from a bean to a walnut. The epidermal roof is flaccid, wrinkled and thin, and easily disposed to rupture, when a thin, yellowish fluid exudes, which dries

in the form of irregular crusts. This form of bleb formation is most frequently seen on the hands and feet, where they may reach a diameter of 1 inch or more.

A more common change in the pustules, however, is the development around the partially desiccated crust of a reddish, vesicular ring, containing a turbid, puriform secretion; just beyond the border of the raised-up epidermis is a narrow, pinkish band, which indicates the spreading edge. These flat, bullous patches spread peripherally, lifting up the epidermis as extension takes place, until perhaps an area the size of a silver half dollar is reached. Central crusting proceeds concurrently with centrifugal extension. In this manner large, dirty-yellow, irregular, friable crusts are formed. It is not uncommon for most of the pustules on the trunk and extremities to become surrounded by a spreading vesico-pustular ring, producing an extensive secondary

FIG. 47.—Variolous impetigo, showing undermining of the epidermis around the dried pocks; appearing during the decline of the eruption.

eruption. Nearly all patients with unmodified smallpox present these "sores" upon the skin. Where the eruption is profuse there may be considerable elevation of temperature and other evidences of septicemia. Indeed, this extensive secondary skin involvement may even cause death.

One of the patients at the Philadelphia Hospital for Contagious Diseases, a woman, aged sixty years, was apparently recovering from smallpox when an extensive outbreak of the character described developed and led to a fatal termination. The crusts in this case were numerous and voluminous and left, after removal by unguentous applications, large areas of denuded skin.

Microscopic and cultural examination of the contents of variolous vesicles and pustules demonstrates that the ordinary pyogenic organisms are absent in the early stages of the lesions, but commonly appear during the late pustular period.

In a bacteriological study of the vesicles and pustules of smallpox[1] we found the lesions to be sterile until a late stage of the eruption. Of 34 cultures of fluid from variolous lesions before the seventh day of the eruption, 33 remained sterile. And even on the eighth, ninth and tenth days bacteria cultivable on ordinary media are not infrequently absent. Of a total of 82 cultures made, 64, or 77 per cent, failed to show any growth whatsoever. Frequently, thick, creamy pus was deposited upon nutrient media without giving rise to any colonies whatsoever. These results, which are in accord with most similar investigations, suggest that the *causa causans* of smallpox, which is, of course, resident in the lesions, is itself pyogenic, and that it is responsible for the suppuration of the variolous pock. Suppuration is, therefore, to be regarded as a part of the normal evolution of the eruption of smallpox. After the eighth or ninth day of the eruption, however, it would appear that a secondary infection, with germs commonly present on the skin, takes place. At this time variolous impetigo develops. The thin, seropurulent fluid in the impetigo blebs, when examined in smear, is seen to contain myriads of microörganisms, chiefly streptococci, although staphylococci and a pseudo-diphtheria bacillus are also found. Cultures of this fluid or of the material from the flat impetigo lesion around the variolous crusts invariably give rise to growths of these several organisms alone or combined. Fluid from a large bleb was injected beneath the skin of a dog; in a few days a local tumefaction the size of a walnut developed, which became surmounted by a dime-sized bleb. This ruptured and left a superficial ulceration. The swelling disappeared and recovery occurred without any further local or general symptoms. When death occurs in smallpox streptococci may in the vast majority of instances be recovered from the heart and other internal organisms. Most of the deaths in smallpox occur from septicemia from the ninth to the eleventh day of the eruption.

As is well known, the commonest complications of smallpox are boils and subcutaneous abscesses. Seldom does a well-marked case of variola vera finish its course without being accompanied by furuncles and phlegmonous infiltrations. We have been impressed with the fact that the tendency to these complications is increased by a preëxistent severe variolous impetigo.

Cutaneous gangrene occasionally occurs during the course of smallpox; we observed this complication about a half dozen times in the Philadelphia Hospital for Contagious Diseases during the epidemic of 1901–1904. These cases are commonly preceded by an extensive impetigo variolosa.

The statement appears to be justified that impetigo variolosa increases the liability to the deeper pyogenic infections, such as boils, abscesses, erysipelas and cutaneous gangrene. It, moreover, appears

[1] Schamberg: Preliminary Report of a Study of the Contents of the Vesicles and Pustules of Smallpox, Jour. Am. Med. Assn., February 14, 1903.

to bear a relationship in many cases to the development of certain postvariolous rashes presently to be described.

It has been our practice at the Philadelphia Hospital for Contagious Diseases to give antiseptic baths to smallpox patients during the late suppurative stage of the disease. The patient is immersed for fifteen or twenty minutes in a bath consisting of a 1 to 10,000 to 1 to 20,000 solution of corrosive sublimate. In other cases we have employed a 1 to 500 solution of creolin. After the bath the patient is dusted with weak antiseptic powders. This course of treatment has a beneficial influence in drying up the impetigo sores and in lessening the tendency to deeper infection.

FIG. 48.—Gangrene of the skin accompanying a severe smallpox; ultimate recovery.

Secondary Toxic or Septic Rashes. Another secondary eruption in smallpox, to which but little reference has been made in literature, is the toxic or septic rash which appears in a certain percentage of cases during the stage of decrustation. Between the eighth and eighteenth days, and most commonly on the thirteenth or fourteenth, there develops upon the trunk, extremities, and at times the face, a peculiar erythematous efflorescence. In most instances the rash consists of a diffuse, dusky redness bearing a strong resemblance to the exanthem of scarlet fever (*scarlatiniform erythema*). At times it is mottled and inclined to become somewhat morbilliform in appearance. The scarlatiniform eruption is peculiar in that the skin immediately surrounding the drying pocks is often exempted, producing a sort of anemic halo. The rash lasts for two or three days and then fades away. If the ery-

thema has been well marked it is prone to be followed by desquamation, which may be most profuse in character. The exfoliation of the epidermis is usually rapid, and may be out of proportion to the intensity of the rash. In one patient the eruption was quite indistinguishable from that of scarlatina. In occasional instances a most inordinate and persistent desquamation follows. A young lad developed on the fourteenth day of the smallpox eruption a severe, deep-red erythema, which was followed by repeated exfoliation of the epidermis. This patient desquamated four or five distinct times, the whole process extending over a period of six or eight weeks. Handfuls of scales could be daily gathered from his bed. The hair of the scalp and eyebrows and the finger-nails were subsequently lost. Another patient in the hospital passed through an almost identical attack. Such cases merit the designation of *dermatitis exfoliative variolosa*.

In rare instances these secondary rashes may become hemorrhagic. Hemic extravasation into the skin is most apt to occur upon the lower extremities, where the stasis in the vessels is greater owing to gravity.

We have seen a severe secondary *purpuric rash*, the history of which is of sufficient importance to warrant its presentation:

H. W., an unvaccinated boy, aged seven and a half years, was admitted to the hospital on September 28, 1901, on the fourth day of the smallpox eruption. The attack was severe, the eruption being semi-confluent. The patient did well for seven or eight days. On the thirteenth day of the eruption the face, on which the swelling had largely subsided, again became tumefied, the temperature rose and a profuse macular eruption, rapidly becoming purpuric, and consisting of bluish-red pin-head- to finger-nail-sized ecchymoses, developed over the trunk and extremities. The patient sank rapidly and died in two days.

The secondary rashes are not infrequently accompanied by rise of temperature. The temperature may suddenly amount to 104° F., decline rapidly, and then remain for some days in the neighborhood of 101° or 102° F. In some patients, with rashes of moderate severity, no pyrexial elevation occurs. While the eruption lasts the patients are, as a rule, somnolent, extremely irritable and considerably prostrated. The rashes are more commonly observed in patients who have had severe smallpox eruptions.

During the epidemic of 1901–1903 we observed these eruptions in perhaps 5 to 8 per cent of all patients admitted. The incidence among children seemed to be greater than among adults. In the severe epidemic of smallpox in 1871–1872 such rashes were much less frequently observed, and in the year 1904 they were distinctly less frequent than in the two preceding years.

The scarlatiniform eruption is the type by far most commonly seen. The resemblance to the rash of scarlet fever is so strong that in the beginning the existence of the latter disease was suspected. In a small-

pox hospital in a neighboring town several patients with scarlatinoid rashes of the character referred to were believed to be suffering from scarlet fever and were promptly isolated. The physician, during a visit to our wards, identified the toxic rashes with the eruption he had observed.

Perhaps some of the cases of scarlet fever associated with smallpox reported by the older writers were in reality instances of scarlatiniform erythema.

In a boy recently treated in the hospital a severe variolous impetigo developed, and this was followed on the fourteenth day of the smallpox eruption by an intense *maculo-papular rash*, which was on the trunk quite indistinguishable from measles; on the face, however, there was relatively little eruption. The duration of the eruption was brief and catarrhal symptoms were absent.

The postvariolous rashes are in all probability septic or toxic in character, due doubtless to the absorption of some poison into the blood. Our experience in the Philadelphia Hospital for Contagious Diseases would indicate that these are more common in patients who have been the subjects of an abundant impetigo.

As far as we have been able to ascertain, none of the modern text-books or monographs on smallpox, save the article by Moore, make mention of these rashes. The earlier writers doubtless regarded the development of the erythema as evidence of an intercurrent scarlet fever, and the numerous instances of the coincidence of these two diseases may thus be accounted for.

Simon,[1] in an article on scarlatina and scarlatiniform eruptions in the course of smallpox, written in 1873, carefully distinguished these two conditions and reported cases representing both true scarlet fever and the secondary erythema which resembles it. In the latter cases he considers the diagnosis of scarlet fever excluded by the date of onset of the complication, the absence of adequate invasive symptoms, the mild character of the angina, the absence of or slight character of the desquamation and the non-contagiousness of the condition.

Of 13 cases of secondary rash, Simon observed 9 develop after the tenth day of the variolous eruption. A few were seen as early as the sixth day and as late as the eighteenth or twentieth day. Simon does not seem to have encountered the profuse desquamation which has occurred in some of our cases. No mention is made by him of morbilliform rashes.

According to Simon, Fleischmann also saw some of these cases, as did likewise Bernouilli, who states that in 1865 he saw a case of secondary erythema in variola which he erroneously regarded as an intercurrent attack of scarlet fever.

[1] Ueber Scharlach und Schlarach-aehnliche-ausschläge im Verlauf der Variola, Arch. f. Dermat. u. Syph., 1873, p. 115.

THE VARIETIES OF SMALLPOX.

The course just described relates more particularly to that form of the disease in which the eruption is either *discrete* or *semi-confluent*. In our experience the vast majority of cases met with belong to the last-named variety, that is to say, the eruption is usually either partially or wholly confluent on the face, the dorsal surfaces of the hands and the lower portions of the forearms, while on the trunk and extremities it is discrete, save a few lesions, perhaps, which may coalesce. Variations in the extent of the eruption may reach extreme limits, from a few small pustules, scarcely characteristic enough to enable one to definitely proclaim the variolous nature of the disease, to the most extensive eruption covering the entire cutaneous surface. Between these two extremes there may occur numerous grades of intermediate severity.

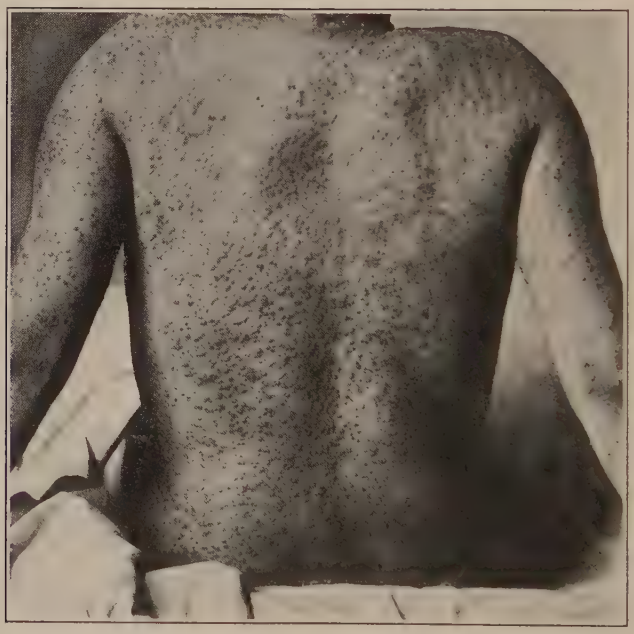


FIG. 49.—Severe smallpox in an unvaccinated man.

Confluent Smallpox (Variola Confluens).—It can hardly be said that there is any symptom during the initial stage of smallpox peculiar to the confluent form of the disease. Inasmuch, however, as the symptoms preceding this type of variola are, with great uniformity, of a severe character, this grave form may be excluded in the presence of mild initial manifestations. Most prominent among the early symptoms are severe headache, persistent retching and vomiting, delirium, or, in children, stupor, violent pain in the back and high fever. The

temperature always rises rapidly, and attains frequently an extraordinary height. It is not at all uncommon for the fever to reach 105° or 106° F., and cases have been recorded in which a temperature of 110° F. was registered. On the third, fourth or fifth day of the eruption the temperature declines, but this remission is never as complete as in milder cases, nor does it continue as long. During the remission the temperature is not far from 101° or 102° F., at which point it is apt to remain for a period of two or three days, when the secondary rise commences. The fever during the stage of suppuration is not usually as intense as in the initial stage, yet it may at times rise considerably higher. The chart shown upon page 205 illustrates the temperature curve of a severe case of confluent smallpox, and may be taken as a fair type of the cases of this class. It may be well to add that the temperature in the suppurative stage was somewhat influenced by the use of antipyretics.

FIG. 50.—Semi-confluent smallpox in an unvaccinated man. Eighth day of eruption.

It is sometimes stated that the eruption of confluent smallpox develops early, often on the second day of the initial fever. Our experience leads us to believe that this variety develops less rapidly than in modified forms of the disease, but there is a shorter interval between the time of its appearance on the face and on other portions of the body. So quickly is the eruption diffused over the whole body that it has been mistaken in the papular stage for measles. Indeed, it is the confluent form of variola which is particularly apt to be confounded with mor-

billi. Ordinarily in forty-eight hours the efflorescence has covered the entire body surface. Owing to the extensive involvement of the skin, redness and swelling begin early. The face is intensely hyperemic and the seat of distressing burning and itching. The marked suffusion of the countenance frequently enables one to prophesy that the disease will take the confluent form. As the eruption progresses it passes through the usual stages, though somewhat more slowly than in the milder cases. The papules are thickly set, and even at this stage a coalescence of lesions may be noted. The skin is thickened and indurated, and feels like embossed leather. Soon the grayish outlines of the vesicles make their appearance and the confluent aspect of the exanthem becomes accentuated. With the conversion of the vesicular contents into pus, great swelling and edema develop, particularly about the face and scalp. The eyelids are enormously puffed, and the margin of the upper lid so greatly thickened that it completely overlaps the lower. The nose, lips and ears are swollen and distorted, imparting to the countenance a most hideous expression. The transformation of the features is so rapid and complete that nurses and physicians who are off duty for a day or two are frequently unable to identify such patients on their return to the wards. The hands and feet are swollen to double their natural size and are most exquisitely tender and painful. When full pustulation is established the neighboring lesions coalesce and form large, flat blebs. In severe cases the walls of the pustules are completely swept away, producing flat, purulent, pasty-looking infiltrations of enormous proportions. When the pus exudes upon the surface and dries a most disgusting stench arises from the body.

In favorable cases, with the beginning of desiccation, a subsidence in the edema takes place, and the crusts are cast off from the skin. The decrustation is, however, slower than in the discrete and semi-confluent forms of the disease. The suppurative process is deeper and more persistent, and may lead to the consecutive production in the same areas of large crusts which are successively thrown off as they form. Owing to the greater depth of the purulent inflammation in the integument, more extensively destruction of the true skin occurs and consequently the scarring is deeper and more conspicuous. Instead of discrete pits the face may be seamed with scars in a most frightful manner.

In severe cases which are going to terminate fatally the course pursued is rather different from that above described. The evolution of the eruption is excessively slow, the lesions appearing to be suppressed and accompanied by but little swelling. The face has a peculiar blurred appearance. The older writers regarded the swelling of the face as a favorable sign, inasmuch as it indicated a certain vigor of the constitution. Physicians who have had experience with smallpox will recognize the correctness of this observation. Swelling of the features is to be welcomed as a favorable indication, and the absence of edema in confluent eruptions must be regarded with grave foreboding.

An ominous sign in these cases is the early development of flat, brownish, depressed scabs on a few of the vesicles on the forehead and cheeks. In these suppressed eruptions the vesicles are only partially filled with fluid, and the features are only slightly swollen; the skin is roughened and presents a somewhat parchmenty appearance. There is most profound prostration, and death results in almost every case.

In confluent smallpox the mucous membrane of the mouth, throat and nose is always severely involved. The epithelium of these parts frequently becomes so completely disorganized by the eruptive process that it presents the appearance of diphtheritic membrane. Swelling of the tonsils and soft palate is often so great as to cause the greatest difficulty in swallowing. It is in the intensely confluent cases that *glossitis variolosa* is apt to occur. The parotid gland sometimes becomes acutely inflamed, perhaps by extension along the ducts of Steno. Profuse expectoration of saliva is not infrequently noted. The pharynx and larynx are almost always the seat of an extensive eruption, giving rise to dysphagia, hoarseness and aphonia. Acute edema of the glottis is one of the most serious accidents to which this form of the disease is liable; when it develops the patient's life is placed in imminent danger. At a somewhat later period serious submucous infiltrations of pus may develop, producing tonsillar or postpharyngeal abscesses or perichondritis of the larynx.

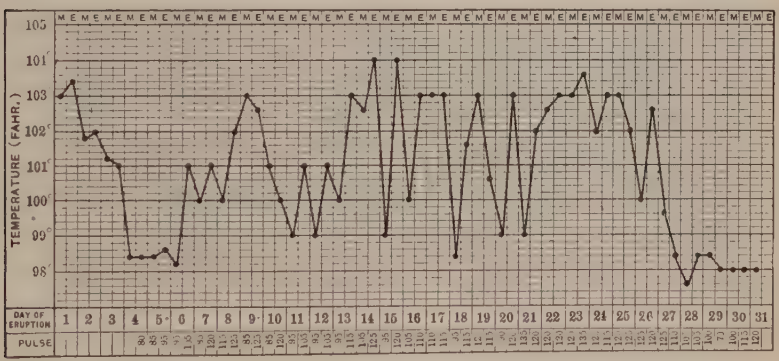


FIG. 51.—W. F., aged thirty-seven years. Case of smallpox in an unvaccinated man, showing the rise of temperature in the initial stage; the secondary or suppurative fever, and a later irregular fever due to abscesses and cellulitis; recovery.

The constitutional symptoms during the suppurative stage of confluent variola are most pronounced. There is marked pyrexia (104° to 105° F.), rapid pulse, frequent cough and expectoration, great restlessness, inability to sleep and profound prostration. Delirium is very common, but the patient does not become maniacal as he often does earlier in the disease. At this stage, also, complications are liable to occur, such as corneal ulcer, keratitis, pleurisy, empyema, suppuration of the joints, cellulitis, phlegmonous inflammations and gangrene of

the skin. Vomiting and diarrhea may supervene, and still further exhaust the patient's ebbing vitality. In fatal cases the patient sinks into a comatose condition, the pulse becomes excessively rapid and the temperature not infrequently rises to 105°, 106° or 107° F. Thus closes the final chapter in one of the most distressing, cruel and frightful diseases "to which human flesh is heir."

The mortality-rate in confluent smallpox varies in different epidemics but it is always extremely high. In general terms it may be stated that at least one-half of such cases perish. When this form of the disease terminates in recovery it is only after a long and tedious convalescence, interrupted by the development of boils, abscesses and other complications.

FIG. 52.—Hemorrhagic smallpox in a puerperal woman. Cutaneous surface covered with petechiæ and ecchymoses. A few ill-formed papules were present.

Hemorrhagic Smallpox.—Of all the forms of variola the hemorrhagic is the most formidable and malignant. For those who contract a well-marked attack of this type of the disease there is absolutely no hope.

According as the hemorrhage precedes or follows the appearance of the variolous lesions, two varieties are distinguished: (1) The so-called *purpura variolosa*, in which the hemorrhage is the primary exanthem; (2) *variola pustulosa hæmorrhagica*, in which it comes on secondarily.

In certain epidemics a petechial eruption is frequently seen at the close of the initial stage of the disease, at or about the time when the eruption should appear. This symptom often precedes the purpuric or hemorrhagic form of the disease, and is therefore, as a rule, an early sign of malignancy. At other times petechiæ and ecchymoses appear

between the papules or vesicles, or develop actually in the bases of these lesions. The vesicles and pustules may contain purulent material or may fill up with sanguino-purulent fluid. Considerable diversity of appearance is sometimes manifested in the eruption of a single case.

There is no satisfactory explanation at hand to elucidate the causation of hemorrhagic smallpox. It would appear that the determining factor is largely resident in the individual, inasmuch as such cases may be derived from ordinary smallpox, and, on the other hand, may give rise to the usual forms in other people. The frequency of this form of the disease varies in different epidemics, being commonest when a more malignant type of the disease prevails. It is well known, for example, that hemorrhagic variola was exceptionally common during the virulent pandemic of smallpox in 1871–1872.

Variola Purpurica.—Variola purpurica, or *purpura variolosa*, is the gravest and most malignant form that smallpox can assume. Zuelzer has called attention to the observation that the period of incubation in hemorrhagic smallpox is not infrequently abridged to six or eight days. The initial stage does not differ essentially from that of ordinary variola. The patient suffers from chill, fever and headache, although the temperature is not as likely to reach so extraordinary a height as in confluent smallpox. The pain in the back is usually violent, and prostration excessive. Furthermore, the patient often suffers from precordial distress and from severe retching and vomiting. The vomiting in this form of the disease is a most distressing symptom, and commonly proves more persistent than in ordinary smallpox. It not infrequently continues for several days after the appearance of the exanthem. Toward the end of the initial stage a diffuse efflorescence appears on various parts of the trunk and extremities, while the face remains for a time exempt. The rash is at first scarlatinoid in appearance and disappears partially under digital pressure; later it becomes more intense and of a deeper hue, and hemorrhagic extravasation into the skin occurs. Petechiæ, vibices and ecchymoses develop upon the chest, axillæ, lower portion of the abdomen, the groins and legs; the dark red or purplish discoloration now present no longer fades away under pressure of the finger. The discoloration rapidly extends to the face, which becomes dusky red or livid and swollen. The conjunctivæ are injected, the eyes bloodshot and the lids bluish, owing to hemorrhage into the cellular tissue. Frequently the extravasation of blood under the conjunctiva covering the sclerotica is so great as to cause this membrane to project beyond the lids, like a sac filled with blood. Under such conditions the patient is unable to completely close the eyes. The cornea retains its normal transparent appearance, but, owing to the elevated conjunctiva about its periphery, appears to be sunken deeply into the eyeball. This condition, together with the dark discoloration of the face and the tumefied features, gives to the patient a peculiarly unnatural expression. A close scrutiny of the skin usually reveals the presence of small abortive vesicles, which may be almost

obscured by the purplish ecchymoses upon which they may be situated. These are most apt to be found upon the forehead, axillæ, groins, or wrists. The vesicles, which are of a plum-colored or leaden-gray tint, never develop to any extent, but remain perfectly flat. As the disease progresses the discoloration of the skin deepens on all parts of the body, giving to the integument a deep indigo hue, which at times almost approaches black. In such cases it is difficult to say, judging from the skin alone, that the patient is not of African origin. Hence, this form of the disease has been known as *black smallpox*, or *variola nigra*.

The eruptive process does not always present unequivocal evidence of smallpox, for there may be complete absence of true variolous lesions. A young woman was admitted to the Philadelphia Hospital for Contagious Diseases, during the spring of 1902, who exhibited upon the skin nothing save a universal scarlatinoid eruption of dusky hue. No vestige of papulation or vesiculation was present. There was hemorrhagic extravasation beneath the sclerotic conjunctiva and bleeding from the mouth, kidneys and uterus. The diagnosis was rendered possible in this patient by the character of the initial illness and the prevalence at the time of an epidemic of smallpox. In another case, observed in a young man some years ago, the eruption consisted of numerous petechiæ and ecchymoses, but no lesions distinctly variolous were present. Such eruptions might readily be confounded with those of malignant scarlatina or measles or purpura hæmorrhagica. Patients presenting manifestations of this character were not uncommonly seen during the very malignant epidemic of 1871–1872.

In this, as in other types of variola, the pharynx and upper part of the respiratory passage participate in the eruption. There is apt to be more or less cough with bloody expectoration. The tongue is large and red and covered with blackish blood crusts, which may also be seen on the lips. A fetor peculiar to this form of the disease is exhaled: it is of a sickening character, and suggests stale or decomposing blood. Purplish spots may be seen upon the gums, palate, tongue and buccal surfaces, but the general mucous membrane is usually pale. Hemorrhages are quite certain to occur from the nose, bronchial mucous membranes, kidneys, rectum and uterus. Vomiting of blood occurs in quite a large percentage of cases, and bloody stools are by no means infrequent. Indeed, blood may issue from any or all of the mucous surfaces of the body; we have even seen a sanguinolent fluid ooze from the eyes. Women almost always suffer from severe metrorrhagia, and if pregnant commonly abort. The temperature is seldom high, usually 100° F. or thereabouts; the pulse, however, is rapid and compressible.

In our experience this type of smallpox occurs most commonly in young and vigorous persons. It is rare in young children and in adults of advanced years. The majority of victims are included between the ages of fifteen and forty years. Unvaccinated pregnant women seem particularly susceptible to this dreadful form of the disease.

One of the most extraordinary features about this hopeless malady is that the mental condition of the patient remains clear almost until the last moment of life. There may be delirium or stupor, but usually the hapless victim faces death with his mind unobscured and his intellect unimpaired.

The course of this type of smallpox is extremely rapid. Death usually takes place from the third to the sixth day of the eruption, commonly as a result of sudden heart failure. Instances have even been recorded in which the patient has succumbed during the initial stage, but such cases must be of excessive rarity. No more terrible disease exists than black smallpox, for from this malady there is no hope of recovery.

Variola Pustulosa Hæmorrhagica.—Hemorrhagic extravasation into the skin may develop at a time during the course of the variolous exanthem. Various types of hemorrhagic smallpox may exist, intermediate between variolous purpura and the pustular hemorrhagic form. Hemic effusion may take place during the papular stage of the disease and may occur in the papules themselves or in the intervening areas of skin. Or the cutaneous hemorrhage may first appear during the period of vesiculation. In this case the vesicles, instead of containing clear serum, fill with a sanguinolent fluid. In other cases the extravasation of blood may be delayed until the pustular stage is reached. The later the hemorrhage is postponed, the more conspicuous are the variolous lesions. The earlier it develops, the more will the true smallpox eruption be suppressed. The amount of swelling and edema is proportionate to the extent and development of the smallpox exanthem. When petechiæ and ecchymoses develop early the skin has a peculiar livid appearance and there is not much swelling. Scattered here and there between the flat, poorly formed vesicles are seen non-elevated, pea-sized or larger, bluish, ecchymotic spots.

The hemorrhagic condition of the pustules may be limited to certain localities, or it may extend over the entire body. Inspection of the legs will often afford the first evidence of this malignant tendency. During the papular or vesicular stage it will be noted that some of the lesions upon the lower extremities are surrounded by a halo of the tint of dilute claret wine. At a later period scattered pustules in this region will be seen to have centers of the color of indigo blue. By degrees others take on the same appearance and the color gradually deepens, until at last in severe cases the pustules on all parts of the body become distinctly hemorrhagic. At the same time livid spots may be seen upon the mucous membrane of the mouth and fauces. The gums are spongy and disposed to bleed. Hemorrhages occur from the nose and internal mucous surfaces, as in purpuric variola.

The temperature hovers about 100° F., but rises higher in the event that the eruption progresses to pustulation. The pulse is rapid and out of proportion in frequency to the moderate febrile movement. As

in the primary hemorrhagic type, the mind commonly remains unclouded almost until the end.

This form of hemorrhagic smallpox is more protracted in its course than variolous purpura, but offers scarcely more hope for the patient. The severity of the prevailing epidemic influences the prognosis to a certain extent. In the malignant epidemic of 1871–1872 patients presenting even mild evidences of the hemorrhagic tendency almost invariably succumbed to the disease. At other times we have seen recovery take place in a few cases, but only among those in whom the hemorrhagic condition of the pustules was limited to a small number of lesions and appeared at a relatively late period of the disease, and in whom hemorrhages from the mucous membrane were not excessive nor long continued.

In June, 1902, a woman, aged twenty-four years, was admitted to the hospital with a most severe smallpox. She had never been successfully vaccinated, although she stated the attempt had been made six times. On admission her appearance was such as to lead us to regard her case as practically hopeless. The eruption was extremely profuse and of a dusky-red color. Upon the legs some of the vesicles showed distinctly bluish centers. On raising the upper lids an extensive subconjunctival hemorrhage was visible in both eyes. The patient was expectorating blood and was bleeding from the uterus and kidneys. On the following day the hemorrhagic symptoms began to subside and the variolous lesions to develop more conspicuously. The hemorrhages gradually ceased and the pustules filled up with a yellowish, puriform material. From this time on the case pursued the usual course of a severe confluent smallpox, the patient finally recovering after a most desperate illness. Special mention is made of this case inasmuch as it is a remarkable exception to the general rule.

We have never known recovery to result where all or nearly all of the vesicles assumed the hemorrhagic character at an early stage, and where there were well-marked epistaxis, hematuria, conjunctival hemorrhage and bloody stools, together with rapid and feeble pulse and the peculiar livid, purplish or indigo color of the skin. Pustular hemorrhagic smallpox is more apt to develop in aged and debilitated subjects, in pregnant women, and in those addicted to the free use of alcohol.

We have occasionally seen distinct hemorrhage into the pustules in the lower extremities of individuals who had a smallpox modified by a remote vaccination. Most of these cases pursued the course of a varioloid and did not appear, to any great extent, to be unfavorably influenced by the bloody extravasation into the lesions.

The prognosis in these cases depends somewhat upon the character of the prevailing type of the disease. Modified eruptions associated with hemorrhage might with propriety be termed *hemorrhagic varioloid*.

Mild Type of Smallpox (Alastrim, Amaas).—In every epidemic of smallpox patients are seen who, though unprotected by vaccination, present remarkably mild manifestations of the disease. The mildness

FIG. 53.—Discrete smallpox in an unvaccinated boy; eighth day of eruption.

FIG. 54.—Same patient as Fig. 53, stage of desiccation; fourteenth day of eruption.

of the symptoms and the paucity of the eruption, may with reason, be attributed to a certain degree of natural insusceptibility to the disease.

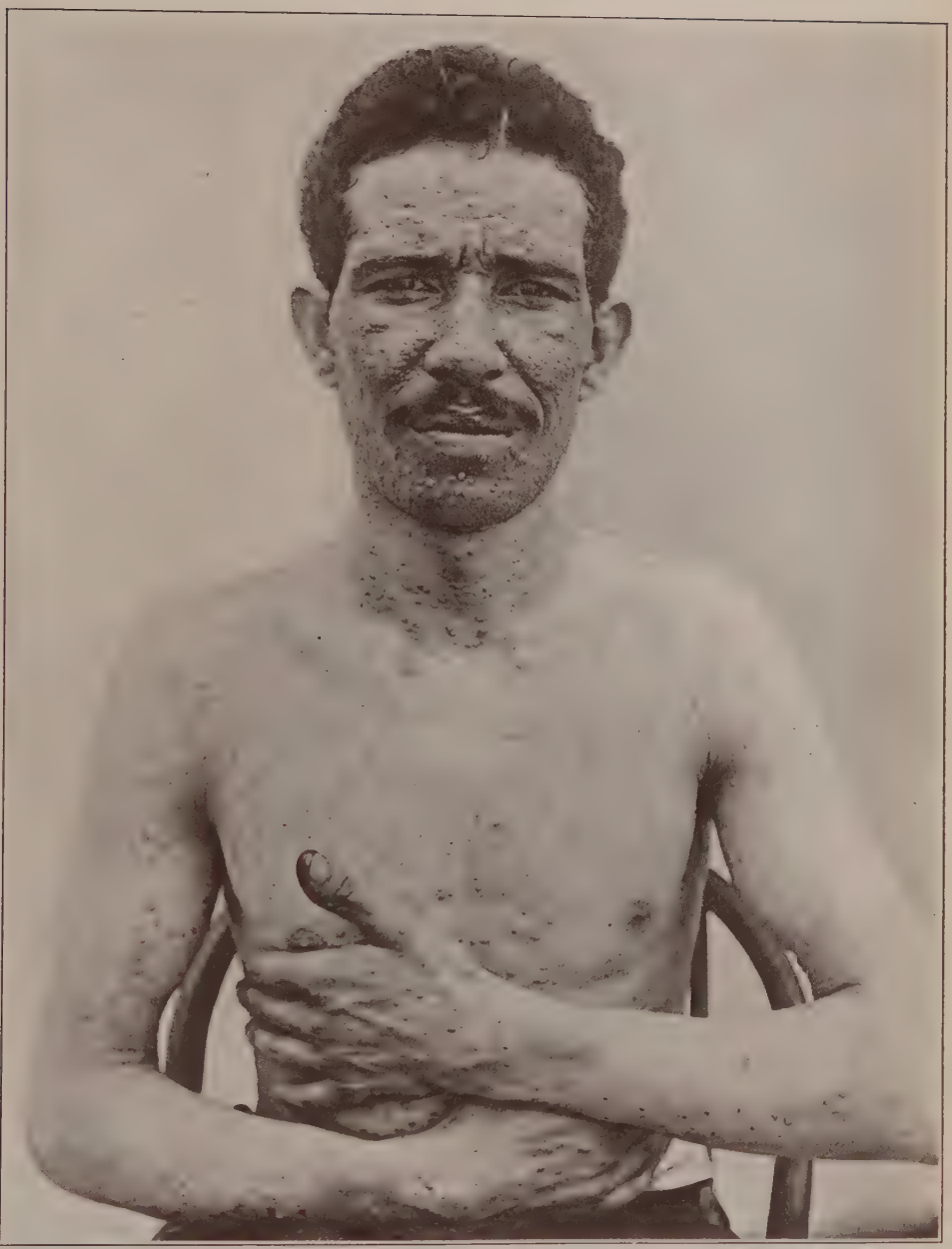
Epidemics of smallpox vary from time to time in their virulence. During the past thirty-one years a remarkable form of "mild smallpox" has been prevailing in the United States, which exhibits certain striking deviations from classic variola. Millions of people have been attacked. It began in Florida in 1896 and was believed to have been imported from Cuba. This form of the disease is doubtless a "sport" resulting from attenuation of the smallpox infection. From Florida

FIG. 55.—Same patient as Fig. 53 after recovering scars and stains present.

it spread throughout the northern, middle and western states and thence to Europe.

The remarkable feature of this disease is that it has continued over so long a period of time that its characteristics have become fixed. A disease extensively prevalent in South America, known as "alastrim" is now recognized to be a mild form of smallpox. It has existed in the West Indies, South America, Africa and possibly in Asia for many years. One of the earliest descriptions is that of Anderson, who described an epidemic in 1865–1866 in Jamaica. There has been considerable diversity of opinion at different times as to the identity of alastrim

PLATE X



Discrete Smallpox Occurring During an Epidemic of the "Mild Type."
Patient Unvaccinated. Seventh Day of Eruption.

and smallpox, but in the opinion of the writers there is no doubt they are basically one and the same disease, due, however, to different strains of the smallpox parasite.

It is characterized not only by a mild course and a remarkably low fatality, but also by a decreased infectivity. Patients once vaccinated, no matter how remotely, appear to be in a large measure immune. A health officer testified before the Pennsylvania State Vaccination Commission in 1912, that negroes vaccinated during the Civil War were

FIG. 56.—Discrete smallpox in an unvaccinated girl. Note that lesions on face further advanced in desiccation that on arms.

protected against the mild type of smallpox to which they were intimately exposed forty-five years later. Its victims are, therefore, almost exclusively unvaccinated subjects. Despite absence of vaccinal protection, it causes only a case fatality of from 0.5 to 2 per cent, very similar, indeed, to the mortality-rate of inoculated smallpox in the eighteenth century. During the year ending June 30, 1902, there there were in the United States 55,857 cases of smallpox with 1852 deaths (a mortality of 3.31 per cent). In the previous year there were

38,506 cases with 689 deaths (a mortality of 1.79 per cent). These figures include smallpox in certain sections of the country where the type was of normal severity.

In the year 1912 two distinct and different types of smallpox prevailed in Pennsylvania. In Carbondale there were 97 cases of the mild type with no deaths; in Pittsburgh, a few hundred miles away, there were 114 cases infected with a European strain of smallpox with 27 per cent mortality. Similarly in England, in 1923, two types were prevailing, a severe type with a mortality of 32 per cent and a mild type with a case mortality of 0.2 per cent. In England, in 1926, there

FIG. 57.—Example of a remarkably mild type of smallpox which has been prevailing for some years in various sections of the United States. Patient unvaccinated.

were 10,179 cases of smallpox with only 18 deaths. These cases obviously in large part represented smallpox of the alastrim type. The disease has spread to Germany, Switzerland and other European countries.

During the years 1898, 1899 and 1900 there were treated in the Philadelphia Hospital for Contagious Diseases under the care of Dr. Welch and Dr. Schamberg 162 patients suffering from this mild type of smallpox. Of this number 138 were unvaccinated, and yet not a single death resulted. Twelve of the patients were white and 150 were negroes.

The onset of this type of smallpox does not differ greatly, except in degree, from that commonly seen in the severer forms of the disease. According to information obtained from many of the patients the entire initial illness was often so mild that they were not obliged to remain constantly in bed; some even stated that they had scarcely been ill at all, and yet on close interrogation it was found that all had suffered to some degree from the usual symptoms. In a few patients the initial stage was marked by its usual severity.

The vast majority of patients would not remain in bed after the eruption appeared. They preferred to don their clothes and indulge in various games. It was a novel sight to see these unvaccinated smallpox patients engage in a game of baseball on the eight or tenth day of eruption, by which time desiccation was often well advanced. Not more than 2 or 3 patients during this epidemic showed symptoms which were at all serious. In some of the mildest cases it was impossible to count as many as a dozen pustules upon the entire cutaneous surface. As a rule, the exanthem was discrete and the lesions sparsely distributed. A few patients, however, exhibited more copious eruptions, even to the extent of producing confluence on the face. In very mild cases the eruption pursued a short, abortive course. Even in the more pronounced cases the duration of the disease was considerably abridged. The course of the disease was identical with that seen in varioloid, and yet in the vast majority of the patients there was no known modifying influence operating such as results from vaccination or a previous attack of the disease.

Among the English cases[1] the incubation period, as far as could be determined, was ten to eighteen days, averaging about fourteen days. *In some instances the incubation may, however, be as long as twenty-one days.* The onset was sudden, with headache, general malaise, fever of 100° to 102° F., pains in the bones and muscles (suggestive of influenza), dizziness, faintness and in some cases gastric disturbances. The symptoms persisted for four or five days (longer than the usual prodromal appearance of the eruption). Only rarely did the eruption become semi-confluent or confluent and pitting seldom occurred.

The older writers described mild epidemics of smallpox many years ago, but in these instances they were of temporary and relatively brief duration.

In 1798 Jenner wrote: "About seven years ago a species of smallpox spread through many of the towns and villages of this part of Gloucestershire. It was of so mild a nature that a fatal instance was scarcely ever heard of, and consequently so little dreaded by the lower orders of the community that they scrupled not to hold the same intercourse with each other as if no infectious disease had been present among them. I never saw nor heard of an instance of its being confluent. The most accurate manner, perhaps, in which I can convey an idea

[1] Watt: Clinical Features of Mild Type of Smallpox, Etc., Pub. Health, 1924, **27**, 197.

of it is by saying that had 50 individuals been taken promiscuously and infected by exposure to this contagion they would have had as mild and light a disease as if they had been inoculated with variolous matter in the usual way. The harmless manner in which it showed itself could not arise from any peculiarity either in the season or the weather, for I watched its progress upward of a year without perceiving any variation in its general appearance. I consider it then as a variety of the smallpox."

Sydenham is said to have described a prototype of the mild variety of smallpox in 1771.

FIG. 58.—A remarkably sparse eruption of smallpox in an unvaccinated girl. This patient had obviously but slight susceptibility to the disease. (Rare.)

Van Swieten, the great Dutch physician of the eighteenth century, wrote in 1759 as follows: "The primary fever is often a little more than a febricula, and the pustules seldom exceed more than from 100 to 200. The form is so mild that secondary fever is not manifested and

constantly is wanting, convalescence coming on on the eighth day of the eruption."

Varioloid (Variola Benigna; Variola Modificata; Modified or Mitigated Smallpox).—The term varioloid, from an etymological point of view, would indicate a disease merely bearing a resemblance to variola. The impression thus conveyed is, of course, a false one, for varioloid is true smallpox in a modified form. This is evident from the fact that the infection arising from this milder form of the disease gives rise to variola vera in unprotected persons. Since the introduction of vaccination varioloid has become much more frequent than in former times. Indeed, in well-vaccinated communities modified smallpox is apt to numerically exceed the cases of ordinary variola.

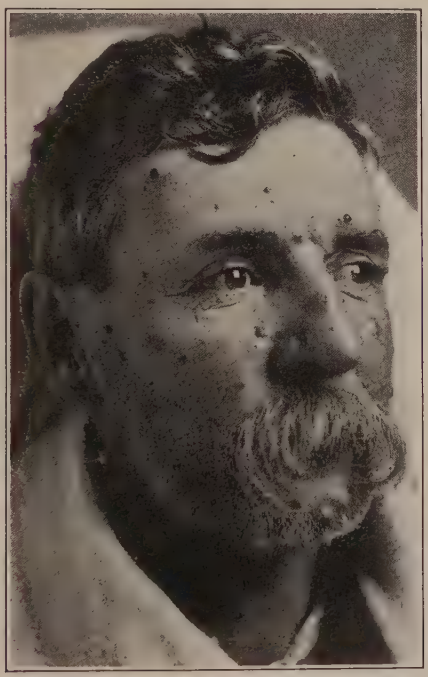


FIG. 59.—Mild case of varioloid in a man vaccinated in infancy.

It is well known that the immunity conferred by vaccination, although complete at first, becomes in the course of time more or less impaired in the vast majority of individuals. The protective influence from this procedure diminishes very gradually for a variable period of time and may ultimately become entirely extinguished. It is readily comprehensible, therefore, that we may encounter vaccinated persons in whom, on the one hand, there is almost complete protection against smallpox, and, on the other, individuals whose susceptibility to small-

pox has quite fully returned. The former, when they contract smallpox, will exhibit the mildest sort of symptoms, with an insignificant eruption, while the latter may develop the most severe confluent or even hemorrhagic variola. Between these two extremes one may encounter almost every possible intermediate grade. It should be stated, however, that it is exceptional for the vaccinal protection to be completely lost. Usually a modifying influence upon the course of the disease will be exerted, even when it appears at the outset that the patient is going to suffer from confluent smallpox. The vast majority of vaccinated persons who contract smallpox have the course of the resulting disease favorably influenced.

We class as varioloid all vaccinated cases in which the eruption is markedly abridged in its course and in which there is but little if any secondary rise of temperature. To be sure, cases in which a second attack of smallpox is favorably influenced by an antecedent one would also deserve this designation. We regard as variola all unvaccinated cases and all those vaccinated cases in which the eruption pursues its regular course, and is attended with secondary or suppurative fever.

There are certain unprotected individuals who possess more or less natural immunity against smallpox and in whom the disease is mild and of short duration. Some writers would include these cases in the category of varioloid, but we prefer to regard them simply as mild forms of variola vera.

We not infrequently meet with cases of smallpox in vaccinated individuals which are so near the dividing line that the determination of the class to which they belong must be postponed until the suppurative stage has passed.

Varioloid cannot always be distinguished in the initial stage from variola vera, since the train of symptoms may be the same and of equal severity in each. In many cases, however, the invasive manifestations in varioloid are extremely mild and will warrant a prediction of a sparse exanthem. Unmodified smallpox is so seldom ushered in with mild symptoms that the likelihood of its occurrence after slight constitutional disturbance is remote. It is important to remember, however that a severe initial illness does not preclude the possibility of the development of varioloid.

The duration of the initial stage in varioloid is subject to considerable variation. While this period in variola lasts quite uniformly three days, in varioloid it may be as short as twenty-four to forty-eight hours, or as long as four or five days. At the commencement of the invasive stage the temperature rises to a variable height; upon the outbreak of the eruption it usually drops rather suddenly to the normal or even below this point. Ordinarily no subsequent rise occurs unless complications develop. In other words, the average case of varioloid is attended with fever only during the initial stage. With the subsidence of the pyrexia there is a general abatement of all of the systemic symptoms. The headache and backache cease, often with agreeable prompt-

ness, and the patient feels quite well again. In every large epidemic of smallpox instances are noted in which artisans and workmen, recovering from the initial stage of a varioloid, resume their daily labors unmindful of the "pimples which have broken out" on them. Mild cases of this character are a fertile source of spread of the disease.

The initial erythematous exanthems, more particularly the morbilliform type, not infrequently develop during the febrile stage of varioloid. Indeed, this prodromal rash, not unlike measles in appearance, is so commonly followed by an exceedingly sparse eruption that it might almost be regarded when present as the forerunner of varioloid.

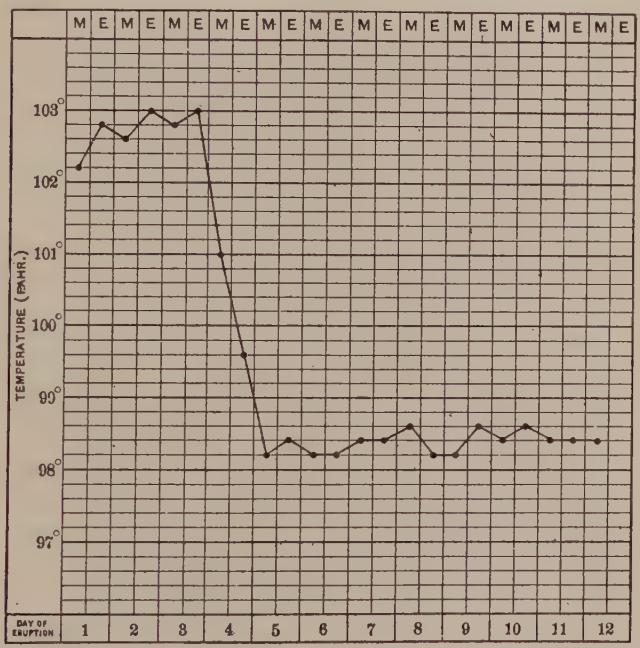


FIG. 60.—W. C., aged twenty-nine years. A case of varioloid, showing the temperature during the initial stage; the fever began to decline upon the appearance of the eruption.

But if the rash should be petechial or purpuric in character it is, as a rule, an indication that the attack will be severe.

The extent of the eruption varies greatly in different cases of varioloid. The protection may be almost but not quite complete, and the patient may pass through the initial stage but remain free of eruption. To this most benignant form of smallpox the term *variola sine exanthemate* or *variola sine variolis* has been given.

There is nothing peculiar about the eruption of varioloid except that it is milder in its course, of shorter duration than that of variola and exhibits various irregularities. It almost always appears on the face

and rapidly spreads to other parts of the body, although at times it makes its appearance on the trunk and extremities quite as early as on the face. The lesions do not develop quite as regularly as in unmodified smallpox, it being not unusual to find some pustules larger and farther advanced than others. The eruption may be limited to a very few lesions on the face and hands, or it may assume a semi-confluent form, and also invade other parts of the body to a considerable extent. We have observed several undoubted cases in which but a single lesion could be found upon the entire cutaneous surface. In the milder forms the lesions do not pass through all the stages, but become abortive and dry up at an early period. In the severer forms the eruption, although confluent or semi-confluent, pursues a distinctly modified course. In such cases the lesions do not penetrate into the deeper layers of the skin, but remain limited to the epidermis. Hence the course of the eruption is shorter, the process of suppuration is abridged and the lesions desiccate early; in addition the crusts are rapidly thrown off and there is little or no scarring. This variety of smallpox was called by the earlier writers "confluent superficial." We have seen vaccinated patients with confluent eruptions which in the beginning looked most formidable and dangerous; but the magic influence of the vaccine disease was fortunately there to convert the serious malady into a comparatively trifling affection.

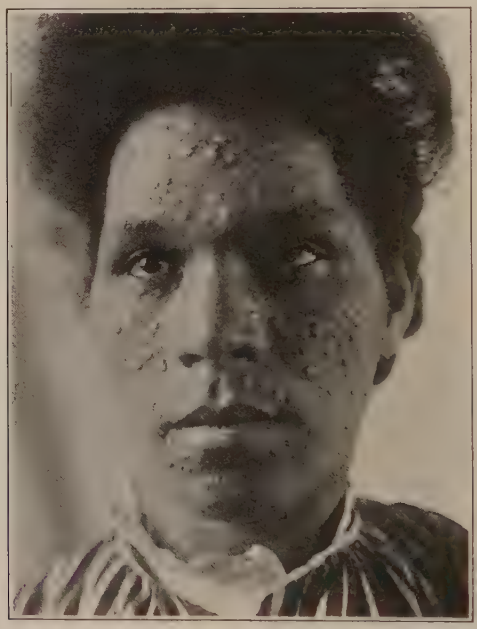


FIG. 61. Tuberculated elevations (variola verrucosa) left after the shedding of the crusts.

More frequently the eruption of varioloid is discrete and sparse, but runs the same mild course. The papules are very early converted into vesicles and reach the pustular stage on the third or fourth day, completing their evolution from the fifth to the seventh day, when desiccation begins. The pustules are frequently acuminate or conical, quite unlike the large, hemispherical pustules seen in unmodified smallpox. They dry up quickly, forming thin, brownish crusts, which fall off much sooner than in the ordinary form of the disease. After decrustation reddish stains, later becoming brown, may be left, but these are not as persistent as in variola vera. Owing to the superficial character of the skin involvement in varioloid, most of the patients escape without any permanent scarring.

When the modification of the eruption is still greater it is not unusual to find that the lesions develop into large, solid, conical papules, having at their apices small vesicles which rapidly desiccate and form thin crusts. After the crusts have fallen off the lesions remain tuberculated for some time. Viewing a patient with this condition from a little distance it is often difficult to say whether the eruption is just beginning or terminating. Sometimes these tubercles present the appearance of warty excrescences; to this form of the eruption the name *variola verrucosa*, or *wart pox*, has been given. This modification of the smallpox eruption is seen usually upon the face. In the course of time the elevations flatten down and disappear, as a rule, without leaving scars. Another somewhat common form of the eruption is that known as *variola miliaris;* in this variety the majority of the vesicles are very small, not larger than millet seeds; without progressing further they turn yellow, desiccate and disappear. Not rarely a few tolerably well-developed pustules are found mixed with these smaller lesions.

Variola corymbosa is a designation applied to those eruptions which exhibit grouping of rather flat pustules in the form of corymbs or clusters. It is alleged by some writers that the mortality-rate is particularly high in cases showing this character of eruption.

The contents of abortive vesicles and pustules frequently desiccate without rupturing, producing hard, horny, convex, shining, reddish-brown crusts. This form is designated *variola cornea*, or *horn pox*. The reddish-brown, horny crusts are quite characteristic of smallpox. They are particularly common in varioloid, and often materially aid one in the diagnosis of doubtful cases. They are of distinct value in cases which are seen for the first time at a late stage, when the original appearance of the eruption is altered. The horny crusts are seen most frequently on the hands and forearms, but may also be noticed at times on the face.

In the form of the eruption termed *variola siliquosa* there is a retrogression of the pustules with absorption of the contents and the production of epidermal cavities filled with air. In addition to the above irregular forms of the smallpox eruption, writers have described other varieties, such as *variola conica, crystallina, emphysematica, fimbriata,*

FIG. 62. —Extremely mild smallpox in an unvaccinated child.

FIG. 63.—Severe smallpox in an unvaccinated child. Unusually extensive eruption on trunk.

lymphatica, pemphigosa, pustularis, rosea, morbillosa, carbunculosa, globulosa, etc.

These various designations do not indicate separate varieties of the disease, but merely different appearances produced by more or less trifling changes in the lesions.

The mucous membrane of the mouth and upper air passages is usually affected in varioloid, but much less severely than in unmodified smallpox. The various complications involving the skin, eye and other organs may occur in varioloid, although they are decidedly less frequent and less severe in this form of the disease. In rare instances grave affections of the brain and spinal cord may complicate mild cases of smallpox; to this more extended reference will be made in considering the complications of variola.

FIG. 64.—Large umbilicated pustules. Seventh day of smallpox eruption.

Inoculated Smallpox.—Although the practice of inoculation of smallpox is completely obsolete and prohibited in most countries by statutory legislation at the present time, it is of interest to know the clinical appearances produced by it. Not having had any practical experience with this form of the disease, we prefer to present the description given by Gregory:

"Inoculation is performed by introducing into the arm at the insertion of the deltoid, by means of a lancet, a minute portion of variolous matter. The thin lymph of a fifth-day vesicle is to be preferred to the well-concocted purulent matter of the eighth-day matter, but both are efficient. One incision only is to be made. On the third or fourth day the punctured point is hard, and a minute vesicle, whose center is depressed, may be observed surmounting an inflamed base. On the fifth day the vesicle is well developed and the areola commences. On the sixth day the patient feels stiffness in the axilla, with pain. The inoculated part has become a hard and inflamed phlegmon. The subjacent cellular membrane has become involved in the inflammatory action. On the evening of the seventh day or early on the eighth day rigors, headache, a fit of syncope, vomiting, an offensive state of the

breath, alternate heats and chills, languor, lassitude, or in the child an epileptic paroxysm, announce the setting in of fever. The constitution has taken alarm and sympathizes with the progress of the local disorder.

"On the appearance of the febrile symptoms the inflammation of the arm spreads rapidly. An areola of irregular shape is soon completed, which displays within it minute confluent vesicles. On the tenth day the arm is hard, tense, shining and very red. The pustules discharge copiously and ulceration has evidently penetrated the whole depth of the corium.

"On the eighth day spots of variolous eruption show themselves in various and often most distant parts of the body. In a very large proportion of cases the eruption is distinct and moderate. Two hundred vesicles are counted a full crop. Sometimes not more than two or three papulæ can be discovered, which perhaps shrivel and dry up without going through the regular process of maturation. At other times the eruption is full and semi-confluent, passing through all of the stages of maturation, scabbing and cicatrization. Between these extremes every possible variety may be observed. The truly confluent eruption with affection of the mucous membrane is rare. Secondary fever, therefore, is not common, at least in any intensity.

Smallpox in the Pregnant Woman.—The functions of the uterus are disturbed with striking frequency during the course of smallpox. The menses quite uniformly appear out of their normal course, and in pregnant women abortion or premature birth is an accident of common occurrence and one that adds greatly to the danger of the disease. Although the premature advent of menstruation and even the occurrence of abortion are not uncommon events in many other infectious diseases, their occurrence in smallpox is so extremely frequent as to suggest a direct relationship with the variolous process. It is probable that abortion is the result of the uterine hemorrhage which is so commonly excited during an attack of smallpox. In some cases it may be due to the death of the fetus which is suffering from an intra-uterine variola.

The symptomatology and course of smallpox are often markedly influenced by the pregnant state. The gravity of the disease is considerably augmented as a result of the coexistence of this condition. Of 113 cases of smallpox in pregnant women treated by Drs. Welch and Schamberg, 35 died, constituting a mortality-rate of about 31 per cent. In unvaccinated women the death-rate was truly frightful, 20 dying out of a total of 27 such cases, giving a mortality-rate of over 74 per cent. Of 85 women vaccinated at some previous remote period, 14 died, the mortality-rate being about 16 per cent.

		Died.	Mortality-rate, per cent.
Smallpox in pregnant women:			
Vaccinated	85	14	16
Unvaccinated	27	20	74
Vaccine condition unknown	1	1	
Total	113	35	30

If abortion occurs during the initial stage the disease is apt to assume the form of purpura variolosa, in which case death is practically inevitable. Not every case in which abortion or premature birth occurs in the earlier stages of the disease takes on this malignant form. In attacks which are considerably modified by previous vaccination, the smallpox process is, of course, not so seriously affected by the occurrence of this accident. Even in cases of true variola, when the loss of blood is not very great, which is rarely the case, the variolous process may pursue its regular course and progress to a favorable termination. In but 5 cases out of 31 did recovery occur, when abortion took place before the tenth day of the eruption.

The gravity of smallpox in pregnant women appears to vary considerably in different epidemics. Dr. Welch and one of the authors had the opportunity of observing these cases in three rather extensive periods of smallpox prevalence.

The mortality-rate in pregnant smallpox women in 1871–1872 was 30.43 per cent; in 1881–1882, 51.61 per cent.; in 1901–1902, 13.8 per cent. Of those that aborted the mortality-rate in 1871–1872 was 37 per cent; in 1881–1882, 68.42 per cent; in 1901–1902, only 15 per cent.

FIG. 65.—Acquired smallpox in a one-month-old unvaccinated infant: fatal.

Smallpox in the Fetus.—During an attack of smallpox the causative germ, in all probability, circulates in the blood stream of the patient. Therefore, when a pregnant woman suffers from variola we would naturally expect the fetus to be likewise attacked and to pass through all of the phases of the disease simultaneously with the mother. Strange to say, however, this is but seldom the case. In a minority of instances the fetus does become infected, but not synchronously with the infection of the mother. Indeed, in most cases in which the fetus develops smallpox it passes through a period of incubation in the same manner as if it were in the outer world; that is to say, about two weeks

elapse from the time the mother shows symptoms until the disease appears in the child. From this observation, which is quite generally the experience of most writers, it would seem that the infant *in utero* ordinarily becomes infected, not through the maternal circulation, but through contact or proximity. If the blood of the mother were the infecting medium the disease in the fetus should be of constant occurrence. There are rare cases in which the fetus contracts smallpox after an exposure to the disease by a mother who happens to be an immune. In such cases it is difficult to understand how the causative agent could reach the infant *in utero* save through the maternal blood.

Smallpox may be communicated to the fetus *in utero* at any time between the fourth month of gestation or possibly earlier and the full term. When infection takes place in the earlier stages of intra-uterine

FIG. 66.—Colored child, born dead at term, with the smallpox eruption present in the stage of pustulation, the mother at the time convalescing from the disease.

life, the fetus usually perishes and is expelled in three or four days, or it may be retained for three or four weeks after life has become extinct. There are well-authenticated instances in which the child suffers and recovers from an intra-uterine attack of smallpox, and is *born at term with variolous scars.*

When the infection takes place during the later periods of pregnancy the child at birth may be covered with the eruption, which may represent any stage of development. This occurrence is so well authenticated that it is unnecessary to quote any cases from literature. We have ourselves met with 4 or 5 instances of this character. In one case a six months' fetus presented a few red spots which evidently resulted from a mild vesicular eruption. In another instance an infant was born at the eighth month, on whose body at birth the eruption was just appearing. In a third case a four months' fetus was expelled on

the thirty-seventh day of the maternal eruption. The eruption on the child was rather sparse, consisting of two whitish, variolous pocks on the sole of the right foot, one on the heel of the left foot, one on the chest, on on the back and two firm lesions upon the palm of each hand.

The fourth case occurred in a colored child (Fig. 66) born at eight months on the thirty-third day of the mother's eruption, the latter suffering only from a very mild varioloid. The infant had evidently been dead for some days, as the horny layer was detached from the underlying skin in large areas. Smallpox lesions in the pustular stage (about fifth or sixth day) were present upon the face, extremities and body, but not profusely. It was calculated that the exanthem in the child began about twenty-seven days after the eruption appeared in the mother.

FIG. 67.—Smallpox contracted *in utero* and appearing nine days after birth; the vaccine lesion seen upon the arm resulted from vaccination on the second day after birth.

The child of a variolous mother may be infected with smallpox *in utero* and be born free of lesions, the eruption appearing some days after birth. If the infant is infected during parturition the outbreak of the eruption may be delayed for a fortnight after it has entered the world. If it is infected earlier the eruption may appear on the first, second or third day of life, or at any period within two weeks. We have observed this phenomenon on numerous occasions. Fig. 67 represents a child born on the first day of the mother's eruption, which was hemorrhagic and rapidly fatal. The infant developed the eruption on the ninth day of its life and succumbed to the disease on the fourteenth day. It was vaccinated on the second day, on admission to

the hospital, and although the vaccination took it was not sufficiently advanced to materially modify the smallpox exanthem.

The frequency of fetal infection does not seem to bear a relationship to the severity of the disease in the mother. Pregnant women suffering from the severest form of confluent variola do not communicate the disease to the fetus more often than those who have the disease in the mildest possible form.

When a pregnant woman undergoes smallpox without miscarriage occurring, the susceptibility to the disease is not destroyed in the infant, except in rare cases. Susceptibility to the vaccine disease, in the vast majority of instances, is, we think, evidence of susceptibility to smallpox. Now and then an infant is born under the circumstances named that will not respond to vaccinia. We have met with three or four such cases.

Concerning the occasional failure of the offspring of variolous mothers to respond to vaccination, it may be said that it is sometimes very difficult, under ordinary conditions, to successfully vaccinate very young infants. In such cases a successful result may sometimes be obtained at a later period, say, at the age of four or five months. This was exemplified in a case reported by Rigden, in which a mother with varioloid gave birth to an infant at term during the height of her eruption. She made a good recovery and was able to nurse her child almost from the day of its birth. The infant was vaccinated the day after its birth, but without success. Between the age of four and five months another attempt was made, with a successful result.

It is of interest to note that in the case just quoted and in our first case the child in each instance was insusceptible at birth to both vaccinia and smallpox. The failure to secure a successful vaccination in our second case may possibly be attributed to the use of inert virus.

But in the vast majority of instances smallpox in the pregnant woman does not destroy the susceptibility to vaccinia in the infant. Our own experience and that of other writers constitute adequate proof of this statement. Rigden[1] reports 6 cases of successful vaccination in infants born of mothers suffering from smallpox. We have in a score or more of instances successfully vaccinated children who were born of variolous mothers; some of these infants were vaccinated as soon as they were born, while others were only successfully vaccinated several months later. A picture of a successful result of a vaccination at birth is shown in Fig. 8 in the chapter on Vaccinia.

When the infection has occurred *in utero* vaccination of the infant at birth frequently mitigates the character of the subsequent eruption. If a week or more elapses between the time of vaccination and the development of the variolous exanthem the lesions are apt to be modified. When the eruption develops within the first week after birth little or no modification is to be expected.

[1] Brit. Med. Jour., February 24, 1877.

THE URINE IN SMALLPOX.

That excellent French physician and teacher, Trousseau, early observed that albumin was frequently found in the urine in smallpox. He says: "Albuminuria is almost as common in confluent smallpox as in scarlet fever. There is this difference, however, that in scarlatina the albuminuria appears during the decline of the disease and in confluent smallpox during the acute period of the disease. Extensive observations by Abeille have shown that in confluent smallpox, as in scarlatina, albuminuria is met with in about one-third of the cases."

The urine was repeatedly examined in 83 patients suffering from variola and in 26 patients with varioloid by Drs. Welch and Schamberg. Of 83 cases of variola, 66.66 per cent showed albumin some time during the course of the disease. Of 28 cases of varioloid, 60 per cent showed albumin during the course of the disease.

That the presence of albumin did not indicate merely a febrile albuminuria is evidenced by the fact that casts were found in a considerable proportion of cases. Surprising to relate, the percentage of cases of varioloid in which casts were found was somewhat greater than of variola; 43 per cent of the 83 cases of variola showed casts in the urine, while of the 28 cases of varioloid, 50 per cent showed casts. The comparative frequency of albumin and casts in fatal cases as contrasted with those that recovered may be seen from the following figures. Of 38 cases of fatal smallpox, 30, or 84.47 per cent, showed albuminuria, and 19, or 50 per cent, showed casts. Of 90 cases that recovered, 45, or 50 per cent, had albumin in the urine, and 41, or 45.55 per cent, showed casts.

It is of interest to note the period at which albumin and casts first appeared in the urine in these cases:

FATAL CASES.

	Albumin.		Casts.	
	Cases.	Per cent.	Cases.	Per cent.
5th day or before	16	52.0	9	47.0
6th to 10th day	9	29.0	7	37.0
11th to 15th "	3	9.7	1	5.5
16th to 20th "	0	0	1	5.5
After 20th "	3	9.7	1	5.5

CASES RECOVERED.

	Albumin.		Casts.	
	Cases	Per cent.	Cases.	Per cent.
5th day or before	24	53.5	11	26.8
6th to 10th day	12	26.6	16	39.0
11th to 15th "	4	8.6	7	17.1
16th to 20th "	4	8.6	5	12.2
After 20th "	1	2.2	2	4.8

It will be seen from the above tables that when albumin is found in the urine it usually appears early. In over one-half of the cases in

which it was present it was first discovered on or before the fifth day of the eruption. The onset of albuminuria seemed to be about the same in fatal cases as in cases ending in recovery. Tube casts when present were also found comparatively early. The tables would indicate than in fatal cases they were present at an early period in a larger percentage of cases than in favorable cases. We desire to point out the fact that albumin and casts, singly and together, may first appear in the urine late in the course of the disease, even when convalescence is established.

Another observation of interest is that the urine from day to day will exhibit striking differences. It will be seen from the appended report of cases that albumin and casts were not present daily from the time of first appearance, but at irregular periods. For instance, in some cases the urine would contain albumin and casts for several consecutive days, then perhaps on alternate days, and then the urine might be free of these for a week or thereabouts, suffering a return a few days later. It is evident that a single examination of the urine under such conditions might readily fail to detect the presence of the abnormal urinary constituents. The persistence of albumin and casts in the urine was also most variable. In some cases they would be present only for a few days and would then permanently disappear. In other cases they would persist for two or three weeks or even longer. In at least two cases, both suffering from smallpox with discrete eruptions, tube casts were present in the urine when the patients were discharged from the hospital. Both of these patients were young men and had not had, to their knowledge, any antecedent kidney disease.

It was not uncommon for tube casts to precede the presence of albumin in the urine and to persist after its disappearance. Indeed, in 7 cases casts were found in the urine when albumin was absent. This observation demonstrates the inadequacy of the albumin test in determining the presence of disease of the kidneys and emphasizes the importance of examining the urinary sediment under the microscope.

The occurrence of uremic seizures in smallpox is extremely uncommon. Convulsions, except during the initial stage, are rarely met with.

To what extent the condition of the kidneys may contribute to the coma that is not infrequently observed in bad cases of confluent smallpox is a question difficult of solution. Edema of the lower extremities is frequently seen during convalescence, but this may be, in at least some measure, attributed to other causes. It may in general be stated that the clinical manifestations of variolous nephritis are much less conspicuous than those characterizing this complication in scarlet fever.

CHAPTER V.

SMALLPOX (*Continued*).

COMPLICATIONS AND SEQUELÆ OF SMALLPOX.

As would be naturally expected, the skin is most commonly the seat of complications in variola. The secondary pyogenic infection of the skin gives rise, as has already been stated, to *impetigo* lesions. These are so common that they have been described under the head of symptomatology. The postvariolous toxic and septic rashes have also been alluded to under this caption.

Boils.—Boils constitute the most frequent complicating disorder met with in smallpox. But few patients pass through an attack of variola vera without suffering from numerous furuncles. The subjects of confluent smallpox suffer more severely than those who have a lighter form of the disease. Even patients with varioloid, however, are not always exempted from this troublesome complication. The furuncles develop most commonly after the stage of decrustation, about the twentieth or twenty-fifth day of the disease.

Subcutaneous Abscesses.—Subcutaneous abscesses are commonly associated with the more superficial furuncular inflammations. These may occur upon any part of the body surface, but involve with predilection the scalp, face, arms and legs. They are often preceded by a cellulitis or a phlegmonous inflammation of the skin and subcutaneous tissues. The patient first experiences soreness and pain in the affected portion of the body. The skin is seen to be swollen, infiltrated and reddened. In the course of several days fluctuation may be detected, and on incision large quantities of pus, even as much as 1 pint may be evacuated. The entire skin of the leg, arm or scalp may be extensively undermined by these accumulations. Besides being very painful, these purulent collections are accompanied by high fever of a septic type. We have known such a fever to continue as long as one hundred and twenty-six days, the patient ultimately recovering. Sometimes an insignificant and, at times, undiscoverable purulent focus will send the temperature up 4° or 5° F., whereas in other patients a large abscess may be present without much febrile disturbance.

In confluent smallpox subcutaneous abscesses may destroy life through the production of an intense septicemia. It is surprising, however, how patients, worn down by a severe and exhausting disease, are frequently able to successfully combat the pus absorption until convalescence is fully established. We recall a young man, who, after a severe attack of smallpox, became the subject of a most protracted

series of abscesses. For six or eight weeks purulent collections, varying in size from a hickory nut to an egg, were almost daily evacuated. The scalp and integument of the face were undermined, the pus communicating with the surface through numerous fistulous openings. No part of the cutaneous surface remained free; in all, this patient suffered from no less than 200 abscesses. Although greatly emaciated he was subsequently restored to health. Fig. 68 shows the *pseudo-keloidal elevations*, made up of hypertrophic granulation tissue, which were left after the healing of the abscesses on the face.

Fig. 68.—Pseudo-keloidal elevations following abscesses upon the face.

Carbuncles.—Carbuncles may develop during convalescence from smallpox, but in our experience they occur with great rarity. We recall a carbuncle which began upon the back of the neck, about the end of the third week, in a patient who suffered from a well-pronounced attack of discrete variola.

Erysipelas.—This complication, when it develops, usually appears at the end of the second or third week of the disease. The face is the region most often affected, although the process may attack the extremities or trunk. At times a diffuse *erysipelatoid inflammation* of the skin occurs without the actual development of a true erysipelas. Both of these conditions are attended with high fever which rises in the evening and remits in the morning. During the epidemic of 1901-1902, among approximately 2000 cases of smallpox, we encountered about 10 instances of erysipelas. Considering the multiple abrasions of the skin, the lowered condition of the patient's vitality and the

almost constant presence of streptococci on the cutaneous surface, it is surprising that erysipelas does not more often attack the smallpox sufferer. Almost all of our patients who contracted erysipelas recovered; some, however, unable in their exhausted condition to withstand the superadded infection, succumbed to the disease.

Bed-sores.—Bed-sores occasionally occur in the course of smallpox, as they do in other protracted diseases. They are far less frequent at the present time than in earlier days. They result from pressure, malnutrition and uncleanliness, and may usually be avoided by careful nursing.

Gangrene.—At times, during the pustular stage of smallpox, the swelling and inflammation of the skin may be so great as to produce multiple areas of necrosis. Sloughing of the skin may also result from undermining of the integument by subcutaneous abscesses.

Apart from these losses of cutaneous tissue, spontaneous gangrene of the skin occasionally occurs during the course of variola. The genitalia are the parts most commonly involved. *Gangrene of the scrotum* is a complication of great gravity, for most patients thus attacked succumb to the disease. It usually manifests itself first as an edematous swelling of the scrotum, which is rapidly followed by gangrene. In extensive cases a considerable part of the integument is lost, exposing to view the testicles, which remain unaffected. When this unfortunate accident develops it begins about the end of the second week of the eruption; it is most likely to develop in bad confluent cases.

Gangrene of the skin is not limited to the regions above mentioned. It may attack almost any portion of the cutaneous surface. During the years 1901 and 1902 we observed 3 cases of gangrene of the scrotum and 5 cases in which gangrene occurred upon various portions of the thigh. In some of the latter cases extensive destruction of the cutaneous, subcutaneous and muscular tissues occurred, the sphacelated areas attaining at times the size of the palm of the hand. In 4 of the 5 cases recovery took place after a tedious convalescence. It may be of interest to note that most, if not all, of these patients suffered from a more or less extensive impetigo variolosa. In the malignant epidemic of smallpox in 1871–1872 neither impetigo, gangrene, nor the septic rashes were encountered as frequently as during the last epidemic (1901–1904). This leads us to emphasize the statement that the character of the disease and the nature and frequency of the associated complications appear to vary greatly in different epidemics.

The Ocular Complications of Variola.[1]—Since Jenner's discovery the destructive effects of smallpox on the ocular tissues have been greatly lessened.

In the analysis of over 2000 cases of smallpox at the Philadelphia Hospital for Contagious Diseases, in 1901–1902, pustulation of the lid

[1] The above section on "Ocular Complications of Variola" was kindly prepared for us by Dr. Burton K. Chance, at that time Assistant Surgeon to Wills Eye Hospital, Philadelphia, and Ophthalmic Surgeon to the Germantown Hospital.

borders was a common affection; conjunctivitis was frequently found with it and was also found independently. There were 36 instances of corneal ulcer, 17 of which were followed by perforation with destruction of one eyeball, and 15 cases were cured without perforation. Of these cases, 15 were in unvaccinated individuals; in 6 others, vaccinated at periods more or less remote, the lesions were less severe; 10 cases of iritis were especially noted.

In taking up the systematic consideration of the action of variola on the various parts of the eye, we find that the skin of the lids is com-

FIG. 69.—Destructive corneal ulcer with panophthalmitis occurring in the latter stage of severe smallpox.

monly a site of the pustular eruption. So much swelling of the tissue may accompany the eruption that the eyes cannot be opened for several days. In such cases severe *conjunctivitis* is usual and often leads to corneal ulceration. The edges of the lids are liable to ulceration and the subsequent cicatrization distorts them, so that styes, misplaced cilia, eversion of the lids, or occlusion of the Meibomian ducts, etc., may result. The lids, like other portions of the skin, after the subsidence of the eruption, may be the seat of abscesses which produce various deformities requiring operation later. As to the mucous membrane of the lacrimal passages, pustules may also form there and give

rise to acute and, later, chronic inflammation of the canal and duct. On the orbital borders periostitis with caries occurs but rarely.

Passing on to the conjunctiva, we find that, as in other febrile diseases, it is commonly affected. Inflammation develops about the fifth day of the eruption; the conjunctiva appears congested and occasionally presents a catarrhal inflammation which is usually of moderate severity and of brief duration, yielding in a few days to treatment. An exception to this appeared in a young man under our care, in whom severe conjunctivitis began on the seventh day, and, in spite of careful treatment, persisted over a month.

The intensity of the ophthalmia is related directly to that of the pustular eruption in general, and more particularly to that of the eruption on the face and eyelids. On the conjunctiva pustules form but

FIG. 70.—Corneal ulceration and panophthalmitis in severe smallpox in an unvaccinated man.

rarely; among the 200 patients with variola, examined by us in 1901 and 1902, they were noticed in only 2 or 3 instances. When they do occur these pustules much resemble in appearance and course the phlyctenular eruption observed in strumous children. They are the size of small lentils, elevated but slightly, and usually situated midway between the corneal margin and the inner and outer canthus. They appear sometimes at the limbus, and when there frequently cause ulceration of the cornea. On the tarsal conjunctiva pustules may be found at the inner fold and on the caruncle, but never at the fornix. In these cases the conjunctival inflammation markedly resembles that of gonorrheal infection; the inflammation is always severe and is accompanied by profuse secretion and chemosis.

Subconjunctival ecchymosis may occur and may produce intense chemosis in hemorrhagic variola. The bacteriological examination of

the conjunctival secretions showed the presence of no specific or hitherto undescribed organisms, but there were present in abundance staphylococci, streptococci and pneumococci.

The cornea, according to other observers, is not subject to the specific lesions of variola, and our experience would lead us to accept this conclusion. Among over 9000 cases of smallpox we have never seen a variolous vesicle or pustule on the cornea. *Ulceration of the cornea* does occur, but it is usually independent of the general process, being rather a consequence of the conjunctival affection. And now, just as in past times, it is the most fruitful cause of blindness as a sequel of variola.

During a period of over thirty-five years but two persons suffering from smallpox have left the Philadelphia Hospital for Contagious Diseases totally blind. Quite a number would, however, have been sightless had recovery taken place.

The corneal complications may arise in two ways: (1) Either without pustules on the conjunctiva or by pustulation, especially when this is at the limbus; (2) at about the fourteenth or fifteenth day of the eruption, during the stage of desiccation, when the infection is transmitted from some broken-down pustules, as, for instance, those of the skin of the eyelids.

The corneal inflammation may be only a slight superficial haze confined to the corneal conjunctiva or Bowman's membrane, or it may extend rapidly and involve the entire membrane. Commonly near the margin of the cornea is seen a small, phlyctenular bleb, filled with clearly fluid, the thin and delicate covering of which is soon macerated by the increased conjunctival discharge, and the vesicle is ruptured, exposing an area of necrotic tissue of grayish color. The symptoms of pain and redness, although usually marked, vary in intensity and duration. As the ulcerated surface spreads the several layers of the cornea are involved until the membrane is perforated, and the aqueous humor escapes and prolapse of the iris follows. At this time the painful symptoms abate. In bad cases pus forms in the anterior chamber or the crystalline lens, and the vitreous humor may be extruded, panophthalmitis developing from a general suppuration of the eyeball, accompanied by great pain, with marked bulging of the lids. Fortunately, the majority of cases present a milder form of keratitis. In this there is only a circumscribed superficial inflammation, which heals promptly and leaves the eye damaged only by the formation of an opacity as the result of the cicatrization of the necrosed area. These scars cause marked irregular astigmatism, which greatly interferes with the acuteness of sight.

In severe cases of confluent variola rapid destruction of the cornea may take place as early as the eighth day. It is usually a forerunner of fatal collapse. In some instances both eyes are affected. As an example of this, 4 patients in our own wards sank rapidly after the destruction of both eyes, at an early stage of the general disease. In

these cases it was noted that the ulceration was preceded by a grayish infiltration of the bulbar subconjunctival tissues; this chemosis rapidly increased, rising above the cornea and surrounding it, choking off its circulation. Immediate destruction of the cornea followed—a true keratomalacia. In certain instances the chemosis is so great as to produce an edema of the subconjunctival and subcutaneous tissues, even to such an extent as to make it almost impossible for the lids to be opened.

It has been our experience to find the ulceration of the cornea less extensive in size and degree in patients who have once been vaccinated; consequently in such persons the healing is more prompt and the sequelæ are less damaging to the integrity of the eyeball.

Parenchymatous keratitis after variola has been reported by but few observers.

The uveal tract is not so frequently affected as the cornea. In our examinations we noted 10 cases of *iritis*, not plastic in form, but of the serous type; it usually manifested itself from about the ninth to the nineteenth day of the eruption. Other observers have noted iritis developing after the subsidence of the general symptoms. Slight pericorneal injection was noticed sometimes in the first week, accompanied by lacrimation, photophobia, tenderness and a small immobile pupil. Although this ciliary irritation may be an independent affection, it is usually a symptom of corneal or iritic disease. It appears to be more frequent in the milder cases, and may persist for a considerable time after the termination of the attack of variola.

Choroiditis was revealed only by the presence of opacities in the anterior or posterior part of the vitreous. We had the opportunity of studying the ocular conditions of a vigorous young man for several weeks after his discharge from the hospital; in each eye were numerous floating vitreous opacities, which rapidly lessened as he regained strength. In none of the cases examined did we find circumscribed choroidal inflammation, nor did we see posterior polar cataract. We can report no cases of glaucoma due to variola nor any cases of retinitis or neuroretinitis. But all these have been reported in the literature of variola by other observers.

In hemorrhagic variola there is no reason to doubt the occurrence of hemorrhages into the retinal sheet, and very probably hemorrhages into the optic nerve may occur. We have not been able to find any such cases reported as actually observed, but Knies is of the opinion that such hemorrhages must have been the cause of some of the affections described as neuritis with and without stasis (choked disk), and with and without termination in atrophy of the optic nerve.

Meningitis as an undoubted sequel is rarely found, but we have come in contact with cases of meningitis for which no logical cause could be found except a remote attack of variola.

Ear Complications.—The pinna of the ear and the external auditory canal frequently exhibit numerous lesions of smallpox. During the

stage of pustulation hearing may be impaired through obstruction of the canal by swelling caused by the presence of the eruption.

Otitis media is occasionally produced by extension of inflammation from the throat along the Eustachian tube. Upon rupture of the tympanic membrane a foul-smelling pus is copiously discharged. One or both ears may be involved. While this complication is rather unusual in adults, it is commonly seen in children. A young boy under our care, suffering from a severe purulent inflammation of the middle ear, developed a *paralysis of the facial nerve* on the same side. This was doubtless due to extension of inflammation to the nerve as it traverses the bony roof of the middle ear.

When otitis media develops it usually manifests itself during the suppurative or desiccative stage. Often before attention is directed to the ear a sharp rise of temperature occurs. More or less permanent impairment of hearing may result from this suppurative inflammation. Writers have recorded instances in which extension of the inflammation has led to caries of the petrous portion of the temporal bone, and in other cases to thrombosis of the sinuses of the brain.

Respiratory Organs.—Reference has already been made to the symptoms produced by the presence of the eruption in the larynx. When the lesions in the neighborhood of the vocal cords are numerous *edema of the glottis* may develop, in which event death almost invariably follows. At a later period of the disease, at times during convalescence, ulceration of the larynx may occur with the production of a *perichondritis laryngeæ*. This complication is fortunately of great rarity.

The presence of variolous lesions in the trachea and bronchial tubes leads to the production, respectively of a *tracheitis* and *bronchitis*, characterized by considerable cough and expectoration of muco-purulent material. These symptoms are present to a moderate extent in most well-pronounced cases of smallpox.

Lobar Pneumonia.—We have found *lobar pneumonia* to be a rather rare complication of smallpox. During the years 1901–1902 we observed but 1 frank case among 2000 patients. *Catarrhal pneumonia* has likewise been infrequent in our experience. A patient who presented for some days a patch of dulness over the base of one lung was, at a late stage of the variolous disease, suddenly seized with severe pain in the chest and great dyspnea; he rapidly sank, and died on the following day. Autopsy disclosed the presence in the lung of a large, egg-sized cavity with a softened and ruptured wall. This probably resulted from the breaking down of a *pulmonary infarct*. The pleural sac contained a considerable quantity of bloody fluid.

Pleurisy.—Of the internal structures, the pleura, perhaps, is most disposed to take on inflammatory action. When pleurisy occurs we usually have the symptoms well marked; yet at times a latent form of the disease may exist, of which the patient makes no complaint, and which may be wholly overlooked until death, when a postmortem

examination will reveal a pleural cavity filled with a sero-purulent material Acute pleurisy occurring during the decline of the eruption sometimes proceeds rapidly to *empyema*. We recall a patient from whom 9 pints of pus were removed by aspiration, but who later succumbed to this complication.

Myocarditis.—It is but natural in a disease of the nature of smallpox that inflammatory and degenerative changes should take place in the heart muscle. The myocardial disease may result from the pyrexia, the variolous poison, or the associated infections, or from a combination of these. *Pericarditis* and *endocarditis* are encountered with great rarity.

Curschmann remarks having seen an ulcerative endocarditis in a case of confluent smallpox. We observed an ulcerative endocarditis on autopsy in a woman who was sent into the hospital with a poorly developed varioloid, and who died a few days after admission. It was evident that the endocardial disease had antedated the smallpox.

Phlebitis.—Phlebitis and venous thrombosis may be met with as a sequel of variola, especially in the lower extremities, giving rise to phlegmasia alba dolens.

Joint Disease.—Joint disease occasionally occurs as a complication, or sequel of smallpox, particularly in children. One or more of the joints may become swollen and painful. The elbows appear most likely to suffer. Chondritis and osteitis may occur, followed by suppuration and destruction of the joint and frequently by death. Neve has reported a number of cases of joint and bone disease following smallpox in children, and we have likewise met with a few such cases.

Abdominal Complications.—Smallpox is singularly exempt from abdominal complications. *Diarrhea* not infrequently occurs as the result of some derangement of the digestive function. While this symptom is usually controllable, it may occasionally be so severe as to precipitate a fatal issue in those greatly weakened.

Peritonitis is a rare complication, and when it occurs may be attributed to some local cause.

Orchitis.—We encountered this complication in perhaps 6 or 8 patients during the first two years of the epidemic of 1901–1904. The swelling may involve the entire scrotum or may be limited to the testicle and epididymis. One or both organs may be affected. The parts often become extremely firm to the touch. The enlargement commonly persists for a few weeks and then gradually subsides, although a variable amount of infiltration may continue for a much longer time. A young man under our care had a severe confluent smallpox, complicated by gangrenous inflammation of the arm, iritis and orchitis. The right testicle was swollen to three times the size of the left. The swelling was firm and not very painful. The infiltration, which extended along the spermatic cord to the external abdominal ring, reached the diameter of an adult thumb. It is said that the analogue of this condition, *ovaritis*, may develop in the female. We have never observed

any symptoms during an attack of smallpox pointing to acute disease of the ovaries.

Phimosis.—Phimosis not infrequently occurs in the pustular stage of smallpox as a result of the swelling of the areolar tissue of the prepuce occasioned by the presence of the eruption. This is seen most commonly in young children.

Nervous System.—Psychic disturbance in the form of *delirium* is not uncommon in the early eruptive period of smallpox. It may in some cases supervene at a later period of the variolous process. The delirium may persist for some days and then disappear, or in rare cases it may develop into a *confusional insanity*. The following cases of insanity after smallpox have come under our observation:

E. M., aged twenty-eight years, was admitted to the Municipal Hospital on November 29, 1903, with smallpox. She bore one good scar from a vaccination in infancy and had a well-marked, discrete variola. On December 6th she was observed to be delirious at times. The mental excitement increased, and the patient became maniacal and had to be strapped in bed. From this time on there were occasional lucid moments, but for the most part the patient was delirious. She would sing and cry and appeared to be completely demented. Despite the fact that the variolous symptoms had quite subsided, the patient continued to lose weight and strength and died in an insane condition, apparently from exhaustion, on January 24, 1904, two months after the onset of the attack of smallpox.

Mrs. A. C. was admitted to the Municipal Hospital on March 10, 1904, with a modified attack of smallpox. She bore two good vaccination scars from infancy. The patient had never exhibited any mental disturbance before the attack of smallpox. Family history negative. On admission the patient exhibited evidences of mental disturbance. She spoke at times rationally, but for the greater part talked incoherently and almost exclusively upon religious topics. Later she became maniacal, jumped from the bed and through an open window; she had to be strapped to her bed to prevent violence. At times refused to eat or drink. She later, when released from her bandages, made several more attempts to jump through the window. She was removed to her home on April 9th, her mental condition having remained unchanged.

Another patient, L. E., aged thirty-seven years, who had recovered from a mild attack of smallpox, developed religious mania after convalescence. He was transferred to a hospital for the insane. It was subsequently ascertained that he had, before his attack of smallpox, suffered from a similar mental disturbance.

Several cases of insanity after smallpox are reported by Seppilli and Maragliano. Of 3 instances referred to, 1 remained permanently insane, the others recovering after appropriate treatment. The authors also record the remarkable case of a violent maniac, who had been confined for about six weeks in an asylum, who during an attack of

confluent smallpox was restored to his senses and after convalescence from variola was discharged from the asylum as a sane man.

Brain symptoms sometimes appear during the stage of decline. We cannot recall a single instance where we have observed clear and indubitable evidence of acute inflammation of this organ, yet we have seen a few cases, perhaps not more than 3, lapse into a state of lethargy or coma, when desquamation had almost completed, without evincing any preceding symptoms of inflammatory action. We have met with a few cases in which there were peculiar psychic changes, followed by *aphasia*. This condition we attributed to the presence of a circumscribed encephalitis. Westphal has called attention to cases of similar nature. In 1872 he presented before the Berlin Medical Society a patient, who during smallpox had had attacks of delirium or coma, followed by a curious disturbance, characterized by slow, measured, scanning speech, and ataxia of the upper and lower extremities, similar to that seen in tabes.

Paralysis.—Various paralyses may develop during the course of variola. We have observed 8 instances of paralysis among about 3000 cases of smallpox. Of this number 5 died and 3 recovered.

In an infant, aged one year and four months, we observed a *hemiplegia* occur upon the first day of the eruption. This succeeded repeated convulsions which took place immediately before and after the appearance of the exanthem. It is probable that this condition was not intimately connected with the variolous process, but resulted from a brain hemorrhage excited by the convulsive paroxysms.

In another patient, a woman, paralytic symptoms appeared during the initial stage of the disease. She was brought into the hospital in a stuporous state, barely able to articulate. There was great difficulty in swallowing and impaired power in the arms and legs; the loss of power in these members subsequently became almost complete, but later a gradual restoration of function occurred. The patient had a most pronounced scanning speech, which was still present when she was discharged from the hospital. The reflexes were markedly exaggerated.

The third patient, a young colored man, had a severe attack of smallpox, complicated by extensive gangrene of the scrotum and penis. At the end of about ten weeks from the onset of the disease he developed partial loss of power in the legs and arms. He could walk with great difficulty with a cane. This condition persisted to the day of his departure from the hospital.

Sometimes the spinal cord is preponderantly or exclusively affected, the symptoms being those of a *paraplegia*. We have observed a half dozen or more instances of this serious complication, of which the following are of especial interest:

Case I.—C. M., aged thirty years, unvaccinated, was seen in consultation on April 22, 1902, on the first day of the smallpox exanthem. The eruption was confluent on the face and hands, and covered thickly all parts of the body.

The pustules began to shrink on the eleventh day; the secondary fever was not high, and there was no delirium. The patient was progressing favorably until May 4th, when it was found that he was unable to void his urine, necessitating catheterization. On the following day paralysis of the lower extremities was noted, sensation being, however, preserved. There was also complete loss of power over the bowels and bladder. Immediately preceding the paralysis there were hebetude and drowsiness, which persisted for several days. A week later, on May 12th, slight motion returned in the legs. A gradual improvement in all of the symptoms then set in. By June 23d the patient was able to walk a few blocks without difficulty, although control over the bladder and rectum was not quite perfect. Complete recovery ultimately resulted.

Case II.—Mrs. N., married, aged nineteen years, was admitted to the hospital with a smallpox of considerable severity. She was progressing well when during the third week of the disease she became unable to move her legs. Sensation was impaired, but not entirely lost. She had loss of control of the bladder and rectum. Within a few days partial motion was restored in the lower limbs. Later diarrhea set in and the patient died.

Case III.—J. W., a man, aged thirty-eight years, was admitted to the hospital on January 13, 1903. He had a scant, modified eruption, having been vaccinated in infancy. About a dozen lesions were present upon the anterior surface of the body, a few were scattered sparsely over the extremities, and on the face there were about fifty lesions. On the eighth day of the eruption the patient developed loss of power in the legs so that he was unable to raise them from the bed. Sensation was impaired, but not lost. There was no pain. The mental condition was good. Later, retention of urine developed, followed after some days by incontinence of urine and feces. The patient died on the thirty-sixth day of the disease, after ten days of high and irregular fever.

Autopsy disclosed the existence of a number of abscesses in the kidneys. A culture from the intradural fluid in the spinal region revealed the presence of staphylococci.

The cord from this patient and from Case II were sent for study to Prof. W. G. Spiller,[1] of the University of Pennsylvania. The spinal cord from Case II had been hardened in alcohol and the microscopic study was, therefore, unsatisfactory, although nothing distinctly abnormal could be detected in the cord.

In regard to Case III Professor Spiller states: "Strictly speaking, the case was one of diffuse myelitis, but with the exception of a part of the thoracic cord the myelitis was almost confined to the anterior horns and was an anterior polyomyelitis, and probably of vascular origin."

[1] Professor Spiller reported the full findings in these cases in a paper entitled A Report of Two Cases of Paraplegia Occurring in Variola, One Being a Case of Anterior Poliomyelitis in an Adult. Other cases in the literature of the subject are referred to (Brain, London, Autumn, 1903).

In 1904 Dr. Charles J. Aldrich[1] reported 3 cases and carefully reviewed the entire subject.

Grave Lesions of the Nervous System Complicating Smallpox With But Scant Eruption.—It would appear that in rare cases the poison of smallpox is largely expended upon the nervous system, the skin escaping with very few lesions. These cases are an exception to the general statement that the gravity of smallpox is proportionate to the extent of the eruption. A remarkable case of this character came under our own observation during the year 1902.

E. M., a burly negro, aged twenty-seven years, was admitted to hospital on April 7, 1902. The patient had never been vaccinated. According to the history, the initial symptoms had been well marked, headache, vomiting, fever and backache having been present. The entire eruption consisted of about a dozen small papules, scattered over the face, forearms, hands and trunk. These were arrested in their development and dried up in a few days, as occurs commonly in cases of varioloid. The patient fell into a state of hebetude after admission, although he had walked to the ambulance. He became progressively more stuporous, had difficulty in swallowing and partial anesthesia and loss of power in the legs. Later, complete paraplegia with incontinence of urine and feces developed. He died on the fourteenth day of the eruption. The temperature on admission (third day of eruption) was 99.2° F.; it later fluctuated for nine days between this point and 101° F., rising to 104° F. just before death.

The diagnosis of smallpox, owing to the poorly developed lesions, was not entirely certain until about ten days later, when the wife and child of the patient were brought into the hospital with variola. Autopsy showed great softening of the spinal cord in the region of the lower dorsal and upper lumbar vertebræ. When the dura over this area was punctured the softened cord ran out like pus. From this portion of the cord a micrococcus was grown on culture. The brain showed no gross changes save an intense congestion of the pia mater.

It is interesting to note that in one of the cases of paraplegia reported by Westphal the patient had an extremely scant eruption and the "disease was so mild that the patient did not go to bed." MacCombie has also called attention to serious disease of the nervous system developing in the course of mild cases of smallpox.

Peripheral Neuritis.—Peripheral neuritis is encountered as a complication or sequel of smallpox with great rarity. In the case of paraplegia, to which we have already referred, in which no microscopic changes were found in the cord, the lesion may have been a peripheral neuritis. Combemale believes the disorders of speech occasionally complicating smallpox to be due to paralysis resulting from the action of toxins upon the peripheral nerves.

[1] Nervous Complications and Sequelæ of Smallpox, Am. Jour. Med. Sci., February, 1904, with full and extensive bibliography.

Disseminated Spinal Sclerosis.—An interesting case of typical infectious disseminated sclerosis is reported by Sottas. A young man, aged eighteen years, with a discrete smallpox eruption, presented during his illness most severe nervous symptoms. The patient was semi-comatose, had a slow dragging speech, nystagmus, general paralysis, atrophy of the muscles of the trunk and limbs and later contractures. At a subsequent date there were characteristic tremors, exaggerated reflexes, incoördination of voluntary movements and great mental excitability.

Septicemia and Pyemia.—Septicemia is commonly observed in the stage of decrustation in confluent smallpox. In severe cases there may occasionally be seen during the third week a high and irregular fever, rapid pulse, low delirium and great prostration, without there being discoverable any pus collection to account for these symptoms. Pyemia is more rare than would be supposed from the writings of the older physicians. Abscesses in the liver, kidney and lungs have been revealed by autopsies, but with great infrequency.

Bone Dystrophies in Variola.—Cathcart[1] reported 2 cases—1 in a girl, aged six years, who had smallpox three years previously and 1 in a young man, aged twenty years, who had had smallpox in childhood. The first patient had deformities of the forearms and wrists, the second a deformity of the right forearm. In the first case the roentgen-ray examination showed areas of decreased density, bowing and thickening of the bones of the forearms and evidence of old necrotic foci in other bones; in the second case decreased density and deformity of the radius and ulna extending beyond the distal head of the radius. Cathcart concludes that in smallpox necrotic foci may be scattered throughout the osseous system, and where the disease is extensive, ossific centers in developing bone may be destroyed and the growth of the bone inhibited, producing deformity.

THE PATHOLOGY OF SMALLPOX.

The Histopathology of the Pock.—The microscopic structure of variolous lesions has been studied by Bärensprung,[2] Auspitz and Basch,[3] Ebstein,[4] Rindfleisch,[5] Unna,[6] Weigert,[7] Touton,[8] Renaut,[9] Leloir,[10] Buri[11] and others.

Weigert regarded the primary changes in the epidermis as necrobiotic and diphtheroid, due to the local effect of the smallpox poison.

[1] Am. Jour. Roentgenol., 1924, **11**, 229.
[2] Die Haut-Krankheiten, 1854.
[3] Virchow's Archiv, vol. **27**, 337.
[4] Ibid., vol. **34**, 598.
[5] Handbuch der pathologische Gewebslehre, 1871.
[6] Virchow's Archiv, vol. **69**, 409.
[7] Anatomie Beiträge zur Lehre von den Pocken, Breslau, 1874, No. 1.
[8] Vergleichende Untersuch. über die Entwick. von Blasen in der Epidermis, 1882.
[9] Arch. de la Dermat. et de Syph., 1881.
[10] Arch. de la physiol. norm. et pathol., 1880, p. 307.
[11] Monats. f. prakt. Dermat., 1892, **14**, 1892.

He claims to have found analogous alterations in the liver, spleen, kidneys and lymph glands, which he believes to be specifically variolous.

Nearly all of the other writers mentioned describe the early changes in the skin as *inflammatory* in character.

Unna[1] has carefully studied the structural changes in the skin, and the following description is condensed from his detailed account:

The development of the variolous vesicle is the result of certain peculiar degenerations of the protoplasm of the epithelial cells. The main features which differentiate the vesicle formation in smallpox from that in chickenpox are the slowness of growth and the prompt addition of suppuration to the epithelial degeneration.

FIG. 71.—Microphotograph of smallpox pustule, showing reticulating epithelial bands. Magnified 80 diameters.

The changes in the protoplasm of the cells of the mucous layers of the epidermis are of two chief varieties. These have been designated by Unna *reticulating* and *ballooning* colliquation (softening). Both are special forms of *fibrinoid degeneration.*

Reticulating colliquation occurs as follows: As a result of the poison of the disease the protoplasm of the cells becomes edematous and undergoes partial or complete liquefaction, thus converting the cell body into a large cavity. Coagulation of the albuminoid bodies set free from the protoplasm now takes place, leading to the formation of a fine granular precipitate which lies on the well-preserved nucleus or the thin, distended cell wall. The nucleus at first remains healthy, but later shows fibrinoid degeneration. When the liquefaction of the cells

[1] Histopathology of Diseases of the Skin, translated from the German by Dr. Norman Walker, 1896.

is partial protoplasmic trabeculæ form which coagulate into a network, often radially arranged, and hold the nucleus and cell mantle together.

The name "reticulating" colliquation is given to this degeneration because of the net-like character of the structure.

This form of degeneration corresponds with the "alteration cavitaire" described by Leloir and Renaut. Leloir maintained that the cavity formation invariably began with a dilatation of the nuclear cavity; in other words, as a result of the liquefaction of the endoplasm.

In the second form of fibrinoid metamorphosis, that designated *ballooning* colliquation, the whole protoplasm of the cell swells up and becomes cloudy and opaque. The prickle projections are withdrawn and the cell becomes rounded. The shape of the cell is largely determined by its position and external pressure, and may be round or flat, biscuit-shaped, pointed, or drawn out into septæ or bands. Most of the cells, however, have the form of hollow spheres or balloons, the predominance of which gives rise to the name "ballooning colliquation."

The reticulating degeneration mainly attacks the older cells, or those in the upper strata of the Malpighian layer, and the ballooning degeneration the younger cells or those in the lower strata. This is accounted for by the fact that the younger epithelia contain a homogeneous protoplasm which readily undergoes homogeneous swelling and coagulation, whereas in the older cells a marginal layer separates from the rest of the protoplasm in its preparation for cornification.

Formation of the Smallpox Vesicle.—During the papular stage the cavity formation begins in the upper prickle-cell layer of the epidermis by a reticulating colliquation of the edematous epithelium. Owing to the slow advance of this process some of the cells are compressed and thus part of the cavity is, from the commencement, divided by septa into a series of segments, the bands running perpendicularly in the center and being directed outward at the periphery.

At the same time the cells of the lower prickle layer undergo ballooning colliquation. The cells lose their prickles and become detached from one another.

As the pock spreads peripherally the differentiation of the process in the upper and lower strata of the prickle layer becomes more marked. In the upper part of the cavity extends laterally many of the marginal cells liquefying and communicating with the general cavity. In the lower part, on the contrary, ballooning and swelling of the cells develop slowly.

At the height of the development, therefore, the pock has the shape of a mushroom, the main cavity formation taking place in the upper projecting parts, while the under half is sharply constricted.

The cavity is completed by extension of the reticulating degeneration downward, particularly upon the periphery, and by the ballooning and detachment of the deeper cells; the latter subsequently become transformed into the compressed bands which traverse the lower portion of the pock.

Umbilication.—Exceptionally a sort of umbilication may result from the accidental piercing of the center of the pock by a hair follicle, the cornified neck of which limits the swelling of the prickle cells. The characteristic depression in the center of the vesicle is due, however, to another cause. It is the result of the reticulating degeneration and edematous swelling of the cells. These occur chiefly at the periphery, whereas the ballooning degeneration which occurs slowly and gives rise to less swelling takes place in the center. The umbilication is, therefore, due rather to a *bulging of the periphery of the vesicle* than to a retraction of the center.

The pressure of the lateral edematous cells is so great as to lead to obliteration of the underlying papillæ, while in the center of the pock before suppuration begins they not only persist but project into the cavity of the pock.

During the vesicular stage the dilatation of the papillary bloodvessels beneath the pock is slight and the emigration of leukocytes is strikingly small. A dense collection of plasma cells is seen in the sheaths of the vessels and increases in number as the vesicle matures. This abundance of plasma cells is remarkable, considering the acuteness of the process, and is only found among the pock-like processes in variola itself.

After the fifth day the bloodvessels, superficial and deep, become distinctly dilated and a stream of leukocytes is poured out, doubtless attracted by the dead germs in the tissues. The margin between the corium and epidermis is so densely packed as to be scarcely recognizable. The cavity of the pock gradually fills up completely with these white blood cells. If the horny roof holds the mass is converted almost into solid tissue; if it ruptures there is more or less profuse suppuration, leading to the formation of crusts.

The primary pustulation is due to the variolous poison, but prolonged suppuration must be ascribed to secondary pyogenic infection.

Healing.—Even before the contents of the pustule are completely dry, a thin layer of epithelial cells lying close on the connective tissue extends from all sides under the pustule.

When the scab is thrown off there is displayed a persistent trough-like depression. Where the scab does not to any great extent depress the base of the pock the papillary layer is not completely flattened out and the scar is not so deeply excavated.

"The depth of the scar consequently depends on the degree and duration of the flattening of the base of the pock beneath the pustule and the scab, and we see therefore that the rational treatment to avoid scars should be mainly directed to the aborting of the pustular stage and the rapid removal of the scab by profuse epithelial new growth. . . . Suppuration alone causes no necrosis of the papillary body, but it may, if profuse, lead to a more rapid casting off of the scab, and thus indirectly to the freeing of the base of the pock; the profusely suppurating cases of smallpox are not those which leave the worst

scars. No doubt prolonged suppuration, coupled with inappropriate treatment, scratching, etc., may lead in many cases to a purulent sequestration of parts of the cutis and thus to distinct scar formation."

For a long time the bloodvessels and all the lymph spaces of the cutis are dilated, and wandering cells and pigment are more abundant than normal.

The pocks upon the *palms* of the hands and *soles* of the feet develop in a somewhat different manner from those elsewhere. The reticulating and ballooning degenerations are only imperfectly seen here.

The "pock body" is usually fan-shaped, undergoes a drier degeneration, and has a horny character. It is usually more superficially situated in the epidermis.

Stokes[1] believes that "the primary exudation of plasma cells has not been sufficiently emphasized by Unna. These plasma cells are probably derived in part from proliferation of the endothelial lining of the lymph spaces and bloodvessels. In some sections made from very early cases, the epithelial cells do not show any great injury, but the cutis is swollen and there is increased number of plasma cells in the lymph spaces and around the small bloodvessels. The condition resembles the response to some injury and seems to be the *first change in the skin*, since the various changes in the epithelial cells are not yet present."

In a hemorrhagic case Stokes found the capillaries and lymph spaces greatly distended and numerous hemorrhages present in the connective tissue.

Councilman and his colleagues have found that the earliest form of degeneration takes place in the nuclei of the cells of the rete mucosum. They become swollen, more vesicular and exhibit an increased central clumping of the chromatin. In the lesions leading to vesicle formation there is a reticular degeneration of the cytoplasm, with a more advanced degeneration of the nucleus. The nuclei may lose their form and become irregular and shrivelled, assuming peculiar shapes. Advanced forms of cytoplasmic inclusions are common in the nuclear space and in vacuoles in the protoplasm. The protoplasmic processes connecting the cells disappear, but the periphery of the cells remains and undergoes condensation.

It is this degeneration which causes the peculiar reticular appearance of the early vesicle. It is always better seen in the periphery than in the center of the vesicle. With the increase of the exudate coming from below, the spaces within the cell enlarge, finally rupture and a network is formed by the coalescence of the cell borders. The typical small vesicle is always fan-shaped, with the handle of the fan seated upon the corium.

A later form of degeneration, the ballooning degeneration of Unna, may best be regarded as a hyaline fibrinoid degeneration. The Malpighian cells become swollen, lose their granular character, become homogeneous and refractile and stain more intensely with the acid dyes.

[1] The Pathology of Smallpox, Johns Hopkins Hosp. Bull., August, 1903, No. 149.

The fluid exudate begins early, and in most cases simultaneously with the degeneration. In the smallest visible papule the swelling is due chiefly to the presence of exudate; in no case was degeneration found without evidence of exudation. The early exudate is clear and contains no admixture of cells. Indeed, a conspicuous feature of the smallpox process everywhere is the paucity of cells in the exudate. The cells appear only at a late stage of the process, and are much less than in other degenerations and exudations due to bacterial infection.

It seems probable that the cells appear when the specific character of the process is passed, they being then attracted to the necrosis. Different varieties of leukocytes are present, but the polymorphonuclear neutrophiles predominate. In the late lesions there are accumulations around the vessels of the varieties of lymphoid cells which are so prominent in lesions in the internal organs, and which Unna has identified as plasma cells.

During the process of repair the contents of the pustule undergo condensation from the evaporation or absorption of the fluid, becoming finally changed into a solid granular mass in which nothing can be recognized. A complete regeneration without cicatrization is possible when the lesions are not extensive and do not involve the entire epithelium, and also when the entire epithelium is destroyed over a small area only, the papillary bodies remaining intact. When destructive changes in the corium occur, complete regeneration cannot take place. After recovery the papillæ are absent or very imperfectly developed and the connective tissue beneath has the characteristics of cicatricial tissue.

Councilman, Magrath, and Brinckerhoff believe that Weigert's explanation of the cause of the *umbilication* is correct in many instances. Weigert regarded the umbilication to be due to the diphtheroid degeneration of the epithelium of the center of the vesicle, thus preventing the distention of the center by the exudate; he believed, however, that the hair follicles and sweat ducts also played a part in its formation. The above-mentioned investigators cannot attribute the umbilication to any single cause. In serial sections the presence of hair and sweat glands at the point of umbilication was rarely missed. The hair follicles play a more important role than the sweat glands. Nevertheless, they are not exclusive agents in the umbilication, for lesions are frequently present upon the glans penis. It is suggested that two factors may combine to favor umbilication: a naturally more resistant center (doubtless due to the degenerative changes), and in some cases the presence of a hair follicle or duct which further strengthens the center.

Histology of Purpura Variolosa.—The skin of 4 cases of purpuric variola were examined by Councilman, Magrath, and Brinckerhoff. Although diffuse hemorrhages were present, the skin almost everywhere showed the early changes characteristic of the variolous process. The general condition was that of swelling and reticular degeneration of all of the lower cells of the epidermis. There were large vacuoles

in the cells, but rarely spaces between the cells resulting from their rupture. In the Malpighian layer there was some separation of the cells by the exudate, and in one section the entire epidermis over a small area was separated from the corium. The nuclei were degenerated, shrunken and lay in large spaces.

The corium showed dilatation of the bloodvessels and hemorrhages, chiefly in the papillary layer. The most striking condition found in the corium was the presence of large numbers of streptococci in the bloodvessels and lymphatics and in the tissues. No polymorphonuclear leukocytes were found in the epidermis, and but few in the corium.

Mucous Membranes.—As has been stated in the section on symptomatology, certain of the mucous membranes participate in the variolous process and show the presence of pocks. In general terms it may be said that most of the mucous surfaces to which air has free access may show smallpox lesions. The nasal, lingual, buccal and pharyngeal surfaces commonly show an abundance of lesions. The esophagus often contains pocks, but seldom in its lower third. At autopsy these lesions often appear as slightly excavated ulcers, frequently with attached blood clots.

Although a few of the older writers have described pocks in the *stomach* and *intestines,* it is extremely doubtful whether they occur in these regions. We have, in a number of instances, seen small, punctate hemorrhages in the gastric mucosa, and in one case a small, superficial ulcer, but never any genuine variolous lesions. A catarrhal condition of the gastric and intestinal mucous membrane is not rare. Follicular ulcerations in the intestines have doubtless been mistaken by some observers for smallpox lesions.

About the anus and a little higher in the rectum the remains of pustules are said to be occasionally observed. This must, however, be rare, as Perkins and Pay in 40 carefully performed autopsies failed to find any pocks in these regions. The bladder and urethra are always free of lesions, with the exception of the meatus urinarius.

Councilman, Magrath, and Brickerhoff, from a careful study of the various membranes in smallpox, conclude that "the lesions of the mucous membranes are in degree proportional to the extent and to the severity of those of the skin. At an early stage of development they resemble the lesions of the skin, but, owing to the structure of the mucous membrane the resemblance is lost in the course of their evolution. In the absence of a restraining horny layer, the degenerated epithelial cells are cast off and the vesicle within the epidermis is rarely seen, the pustule never."

The *respiratory tract* is more attacked than any of the internal surfaces. The larynx, as is known, is often severely involved. Pustules and ulcers are often found in the trachea, particularly at the division of the bronchi. They may, moreover, be encountered in the bronchial tubes of the third and fourth order. The small bronchi often exhibit in addition a catarrhal process, with necrosis of the surface epithelium

and fibrinous or purulent inflammation. The lungs not infrequently show small areas of catarrhal pneumonia.

Curschmann aptly says that "true pocks on *serous membranes* are fables belonging to antiquity, but congestion, inflammation and ecchymoses are common."

The meninges and the peritoneum seldom exhibit pathological changes, but the pleural surfaces are not infrequently inflamed.

Stokes[1] in one case found the pleural surfaces dotted with abundant vesicles about the size of No. 6 shot. On microscopic examination they appeared to be large lymph spaces distended with serous fluid.

The solid *abdominal viscera* undergo serious alteration of structure. The *liver* in fatal cases of smallpox is nearly always enlarged, the increase in size in some cases being most pronounced. The surface of the organ and the hepatic tissue upon incision exhibit a coloration much paler than normal. Nearly all writers refer to degenerative changes in the liver varying from cloudy swelling to a more or less intense degeneration. Weigert describes areas of local coagulation necrosis in which are seen nuclear detritus and many degenerated cells without nuclei. Siderey says there is intense congestion with migration of white blood corpuscles and swelling of the endothelial lining of the capillaries; later the liver cells swell and undergo fatty degeneration.

Roger and Garnier[2] made a microscopic study of the liver in 17 smallpox cases. They conclude that variolous hepatitis is usually total and may affect the interstitial or parenchymatous tissue. Fatty hepatitis is said to be the most common, having been found in 6 out of 11 cases of coherent or confluent smallpox. In hemorrhagic smallpox it is, according to these investigators, constant. Necrotic hepatitis is more rare and is characterized by cellular necrosis in limited foci or diffuse bands. This condition was observed alone in 2 cases and in 2 others associated with fatty degeneration. A third variety, hemorrhagic hepatitis, was found in 1 case in a child with congenital variola.

Ponfick and Curschmann both state that in purpura variolosa the liver is normal in size and color and does not exhibit the degenerations above referred to.

According to Ponfick,[3] the *spleen* in those who die early is swollen, soft and of a light-red color. It later resumes its normal appearance except in purpura variolosa, in which variety it is small, hard and dark red, with prominent follicles.

Roger and Weill[4] found the spleen hypertrophied in every one of 16 fatal cases of confluent smallpox. Among 12 hemorrhagic cases it was enlarged in 4 instances. The most interesting microscopic changes are the presence of nucleated red blood corpuscles, and a predominance of mononuclear leukocytes among the white cells.

[1] Loc. cit.
[2] Étude anat. et chim.du foie dans la variole, Arch. de méd. exper., September, 1901.
[3] Ueber die Anat. Veränderungen der innern Organen bei hemor. u. pust. Variola, Berl. klin. Wchnschr., 1872, No. 42.
[4] Les maladies infectieuses, Paris, 1902.

Perkins and Pay[1] noted hemorrhages into the splenic pulp in 6 out of 40 autopsies; 3 of these were cases of purpura variolosa.

The *kidneys*, like the liver, show changes varying from cloudy swelling to fatty degeneration. Arnaud[2] made histological examinations of the kidneys in 13 cases of smallpox. The changes were briefly of two types—an interstitial cell infiltration and lesions of the epithelium of the tubules.

Stokes[3] has made a careful study of the kidneys in variola. Extensive changes were found in every kidney examined. In one case an acute interstitial nephritis, such as described by Councilman in diphtheria and scarlet fever, was found. In one very malignant case the changes noted were as follows: In the glomeruli the capillaries contained clear hyaline material within the lumen. This was due to an actual degeneration of the endothelial lining of the glomerular capillaries. At times the hyaline material formed a large crescentic mass of homogeneous clear material in the capsular space. The epithelium of the convoluted tubules were swollen and the cytoplasm of the cells contained numerous granules. In many of the cells the cytoplasm had completely degenerated into a mass of clear droplets which produced hyaline casts in the lumena of the tubules. The clear droplets took Weigert's stain for fibrin. The *adrenal bodies* were found by Perkins and Pay[4] to frequently show well-marked fatty degeneration of the cells of the medulla.

The *heart* in fatal cases of confluent smallpox is usually relaxed, soft and somewhat enlarged. Microscopically the changes are those of cloudy swelling and fatty degeneration; fragmentation of the muscle fibers is commonly seen.

In purpura variolosa, according to Ponfick, the organ is firm, contracted and of a brownish-red color.

The Lymphatic Glands.—Roger and Weill[5] state that hypertrophy of the glands in variola follows the same rule as splenic enlargement: it is very marked in the pustular variety and slight or absent in the hemorrhagic form. Microscopically the cells found are similar to those seen in variolous bone-marrow; neutrophile myelocytes are notably present and in addition there are some basophile myelocytes and occasionally eosinophiles. Giant cells are also seen, and in hemorrhagic smallpox nucleated red blood corpuscles.

Stokes examined the cervical and bronchial glands in smallpox and found extensive focal necrosis containing an abundance of streptococci.

Bone-marrow.—In 1873 Golgi[6] made a study of the bone-marrow in 10 cases of pustular and 25 cases of hemorrhagic smallpox. In the pustular form he found a great increase of the white cells, while in the hemorrhagic variety he found a great increase of nucleated red cells,

[1] The Etiology and Pathology of Variola, Jour. Med. Res., October, 1903.
[2] Revue de méd., 1898, **18**, 392.
[3] Loc. cit.
[4] Loc. cit.
[5] Maladies infectieuses, p. 721.
[6] Sulle Alterazioni del Midollo del ossa nel variola, Riv. clin. di Bologna, 1873, p. 238.

a distinct diminution of the white cells, some of which were in process of fatty degeneration, and diffuse hemorrhages in the medullary spaces. The medullary tissue was red and almost as fluid as blood.

Chiari[1] found a condition which he designated "osteomyelitis variolosa" in 72 per cent of 22 cases examined. This process is characterized by pea-sized, whitish, grayish or yellowish nodules, widely disseminated in the marrow substance. These consist of epithelioid cells derived from proliferation of the marrow cells. An early necrosis sets in. Chiari regards these focal necroses as due to the specific variolous poison.

Courmont and Montagnard[2] and Roger, Josué and Weill have studied this subject with results which are in accord with those above detailed.

Roger[3] says: "The cellular formula of bone-marrow in variola is as follows: Great predominance of mononuclear cells and relative diminution of polymorphonuclears." The cellular findings are analogous to those of the blood. The marked differences noted by Golgi in the marrow of the pustular and hemorrhagic smallpox were not confirmed by these writers.

The Testicles.—The occasional occurrence of orchitis variolosa has led to a careful microscopic study of the structure of this organ after death.

Chiari found pathological changes in the testicle very frequently among the cases that came to autopsy. The specific variolous change is a focal necrosis similar to that observed in the liver, spleen, kidneys and lymph glands by Weigert. The alteration begins early in the course of the disease, but reaches its height during the suppurative stage. The inflammatory foci are said to be located predominantly and primarily in the interstitial tissue, although Stokes,[4] in an examination of 2 cases, states that the process began as a necrosis of the epithelial cells of the seminiferous tubules.

In 27 examinations of the testicles Perkins and Pay[5] found well-marked necrosis in 8. Examination of the ovaries failed to discover any lesions of this character.

The *brain* and *spinal cord* ordinarily exhibit no structural alteration in smallpox, save at times a moderate amount of congestion and edema. In a small proportion of cases grave changes may occur even in mild cases. To this attention has been called under the heading of Complications of the Nervous System.

Hemorrhagic Smallpox.—The pathological findings in *hemorrhagic* smallpox differ in many respects from those in ordinary cases.

The condition of the spleen, liver and kidneys has already been referred to. It is uncommon to find hemorrhages in such viscera as

[1] Osteomyelitis Variolosa, Ziegler's Beitr. z. pathol. Anat. u. allg. Pathol., 1893, **13**. 13; Ztschr. f. Heilk., vol. **7**, 385.

[2] La moelle osseuse dans la variole, XIII. International Medical Congress, Section on General Pathology, Paris, 1900.

[3] Les maladies infectieuses, p. 700. [4] Loc. cit. [5] Loc. cit.

the liver, kidneys, spleen, brain, etc. On the other hand, the bloody extravasations are very common upon the mucous and serous structures of the body. These are seen as ecchymoses of these surfaces and as free accumulations in the cavities. The pleural and pericardial sacs not infrequently contain bloody fluid or clots and less commonly the peritoneal cavity.

The loose tissue of the anterior and posterior mediastina and the retroperitoneal space often exhibit bloody exudates. Hemorrhage into the kidney structure itself is extremely rare, but it is seen in the renal pelvis and beneath the capsule of the kidney.

Ecchymoses may occur in synovial membranes and free hemorrhage into the cavity of the joints. Zuelzer, cited by Curschmann, speaks of the frequent occurrence of hemorrhages into the sheaths of nerves, but Wagner could not corroborate this observation.

As might be naturally expected from the symptomatology of hemorrhagic smallpox, practically all of the mucous membranes may be involved in the hemorrhagic process. Bleeding may occur from any portion of the alimentary canal, from the mouth to the anus; the same is true of any part of the respiratory mucous membrane, from the nostrils to the lungs; hemorrhagic infarcts may form in the pulmonary tissue.

Subconjunctival hemorrhage is frequent and constitutes a conspicuous and characteristic early symptom of purpura variolosa.

Bloody extravasation into the Fallopian tubes and uterus is extremely common. Hemorrhage into the structure of the testicles and ovaries is rarely seen, although the Graaffian follicles of the latter are said to be occasionally infiltrated with blood.

The Blood.—The *red blood corpuscles*, according to Hayem,[1] undergo greater destruction in smallpox than in any other fever. This is not noted until after the permanent subsidence of the fever. The diminution in the number of the red cells is most pronounced in the hemorrhagic and confluent cases, in which 1,000,000 or 2,000,000 erythrocytes per cubic millimeter may be lost in a very brief period. In hemorrhagic smallpox the anemia comes on more rapidly; in a patient dying on the seventh day, Hayem counted but 2,000,000 corpuscles. There is likewise a reduction of the hemoglobin, and this may be apparent before the cells are diminished in number. Ikeda[2] has also observed pathological types of erythrocytes in purpuric smallpox like normoblasts and polychromatophilia.

Simon[3] has observed a diminution of *platelets* during the febrile stage with an increase during the pustular stage. Ikeda found the platelets markedly decreased in purpuric smallpox.

The *leukocytes* show a slight drop during the first few days of the disease, and this leukopenia lasts to about the second day of the erup-

[1] Du sang et de ses altérations anatomiques, Paris, 1899.
[2] Jour. Am. Med. Assn., 1925, **84**, 1807.
[3] Clinical Diagnosis, Philadelphia, Lea & Febiger, 1922, p. 1100.

tion, when it is followed by leukocytosis varying with the severity of the disease and reaching its height during the pustular stage. In the severe purpuric types, however, there is usually a sudden drop in the leukocytes, evidently due to the depressant effects of the virus upon the bone-marrow and many degenerative forms of polymorphonuclear neutrophiles may be seen.

The *differential leukocyte count* shows typical changes. Early in the disease the polymorphonuclears are relatively and absolutely increased followed later by a decrease with an increase of small lymphocytes. In purpuric smallpox the decrease of polymorphonuclears with an increase of small lymphocytes may be so sudden and severe that the blood picture resembles that of lymphatic leukemia. The eosinophiles show no change in mild cases but in severe cases are relatively decreased in the early stage followed by a slight increase toward convalescence when desquamation is present.

THE PARASITOLOGY OF SMALLPOX.

While it is practically certain that smallpox is caused by a living microbe, and while a large number of various bacteria have been found in vaccine lymph and the cutaneous lesions of the disease, none can be regarded as the cause of smallpox or cowpox, although some, and especially streptococci and staphylococci doubtless play an important part in the production of the secondary fever. The virus is evidently very minute as it is capable of passing through the coarser porcelain filters.

It is quite definitely established that the suppuration of the variolous pock is the result of the causative agent of the disease and is not due to secondary infection with pyogenic organisms. In the vesicular and even in the early pustular stage of the eruption the lesions will commonly be found to contain no bacteria cultivable upon ordinary media. In an investigation of the contents of smallpox vesicles and pustules Schamberg found 33 out of 34 cultures of lesions before the seventh day sterile. In all, cultures were made from 82 lesions in 51 cases of smallpox; of this number 64 cultures remained absolutely sterile. This work is in accord with most of the investigations upon this subject.

Perkins and Pay[1] made 30 cultures from typical variola lesions at all of the various stages from the beginning vesicle to the full development of the ripe pustule. These were all negative with the exception of 4—1 on the eighth day, 1 on the ninth and 2 on the tenth days of the eruption.

After the seventh or eighth day of the eruption various bacteria, chiefly streptococci, may be found in the lesions.

The streptococcus is commonly found in the late pustules of smallpox and in many of the cutaneous complications, such as boils, impetigo, abscesses, erysipelas, gangrene, etc.

[1] Jour. Med. Res., October, 1902.

After death streptococci are found in the cutaneous lesions and in the blood and internal organs in nearly all cases. There would appear to be in many cases an agonal or postmortem diffusion of streptococci throughout the tissues. In 40 autopsies on smallpox patients made by Perkins and Pay streptococci were found distributed throughout the body of 38.

Ewing[1] found streptococci present in about 90 per cent of the skin lesions cultured at autopsy. He also noted the presence of streptococci in the blood after death in every one of 29 cases examined. In 10 cases of varying severity in which the blood was cultured during life the results were negative.

Arnaud[2] found streptococci in the blood during life in 2 cases of hemorrhagic smallpox.

Perkins and Pay[3] examined the blood in 20 cases of smallpox and found streptococci in 11 cases, before or just after death.

Hines obtained streptococci from the lesions in 5 of 20 cases, 2 being hemolytic and 3 non-hemolytic types. Of 17 patients who recovered, streptococci were obtained from the lesions of but 2, or less than 12 per cent. No streptococci were obtained during the vesicular stage. The agglutinin test indicated that the hemolytic streptococci belonged to different groups.

It is evident from the above investigations that the streptococcus is almost constantly found in fatal cases of smallpox. While no one can seriously entertain the idea that its role in smallpox is causal, it is so uniformly present that some writers believe it bears a peculiar relation to the disease differing from most secondary infections.

Many writers regard the streptococcic bacteriemia as the most frefrequent cause of death in smallpox. Councilman[4] says: "As the result of the study of the disease, both by culture of the lesions and organs and by microscopic examination of tissues, we are inclined to regard bacterial infection as a more important agent in bringing about a fatal termination than the specific parasite. . . . The bacteria are chiefly streptococci."

Perkins and Pay, and likewise Councilman, suggest that the streptococci gain entrance to the circulation through the bronchial and pulmonary mucous membranes.

Perkins and Pay found that the pathogenicity of the streptococci isolated was markedly different. Some of the strains killed rabbits in two or three days, while others were without effect. The writers suggest that the failure of antistreptococcus serum prepared from one variety of streptococcus may be thus accounted for.

Grünhagen,[5] in 1872, appears to have been the first to call attention to the presence of *protozoa in variola and vaccinia*. He described in

[1] Proceedings of the New York Pathological Society, May, 1902.
[2] Revue de méd., 1900, p. 303.
[3] Loc. cit.
[4] Jour. Med. Res., February, 1904, p. 358.
[5] Bemerkungen Ueber den Infectionstoff der Vaccin Lymphe, Arch. f. Dermat. u. Syph., 1872, p. 150.

vaccine lymph, clear, refractive, sharply contoured bodies both free and attached to leukocytes.

Renault, in 1881, described peculiar bodies which he believed to be parasites in the epithelial cells of variola and vaccinia.

In 1887 van der Loeff[1] found in a hanging drop of clear vaccine lymph numerous small, round bodies endowed with amœboid movement; later he discovered the same bodies in smallpox pustules.

L. Pfeiffer published a series of papers beginning in 1887, describing the presence in variolous and vaccine lymph of the "monocystis epithelialis," a small, unicellular, rounded body which he regarded as the specific cause of smallpox. These bodies were also found in the epithelial cells of the Malpighian layer and were said to multiply by division and by endogenous spore formation.

In 1892 Guarnieri[2] made a most important contribution to the study of protozoa in variolous affections. He found in the epithelial cells of the skin in smallpox and vaccine vesicles, and in the cells of the cornea inoculated with variolous and vaccine virus, certain bodies which he designated the *cytoryctes variolæ* and the *cytoryctes vaccinæ* respectively. (The name has reference to the alleged devouring of epithelial cells by the parasite and to the formation of clear space about it.)

Guarnieri attempted the cultivation of these protozoa by inoculating the cornea of rabbits and guinea-pigs. At the end of fifty hours the cornea was scraped and the material examined in aqueous humor in a hanging drop. Small, refractile bodies were found which possessed amœboid movements. Upon section of the cornea, bodies varying in size and shape were found in the deeper layers. Multiplication was said to take place by binary division and by gymnospore formation. Bodies exhibiting a mulberry form were described.

Monti confirmed Guarnieri's findings and produced specific lesions in the cornea by inoculation with various tissues from cases of smallpox.

Ruffer and Plummer,[3] in 1894, described the parasite as a small, round body, about four times the size of a staphylococcus, lying generally in a clear vacuole in the protoplasm of the epithelial cells.

Guarnieri's work has since been confirmed by a number of investigators, including Jackson Clark (1894), von Sicherer (1895), Ernst Pfeiffer, Gorini, Lebredo and Wasielewski.[4]

Wasielewski inoculated corneas with sterile substances and various bacteria and yeasts and failed to produce the typical inclusions seen when variolous or vaccine material was employed. He carried the latter inoculations from eye to eye for a number of generations and produced uniform lesions. From the thirty-sixth generation material was taken from the cornea and 7 children vaccinated; of this number, 6 out of the 7 developed typical vaccine lesions.

[1] Monatsh. f. prakt. Dermat., 1887, **6**, 189.
[2] Centralbl. f. Bakteriol., August 25, 1894.
[3] Brit. Med. Jour., June 30, 1894.
[4] Centralbl. f. Bakteriol., 1897, **21**, 901; Ztschr. f. Hyg., 1901, **38**, 212.

Ferroni and Massari[1] inoculated the cornea of rabbits and guinea-pigs with croton oil and India ink and claim to have produced in the epithelial cells numerous small bodies apparently identical with those described by Guarnieri. They believe that the so-called parasites are in reality derived from the nuclei of epithelial cells and from leukocytes.

Salmon,[2] after a careful study of the staining reactions of the bodies, described, likewise opposes the views of Guarnieri. He says: "The pseudo-parasite is not an endogenous formation; it, therefore, of necessity has an extracellular origin, and the little mass of chromatin can have but one origin, namely, the migratory cells." Copeman[3] remarks: "No one can fail to be struck with the truth and completeness of Salmon's explanation of the facts previously observed."

An important article in opposition to Guarnieri's conclusions was contributed by Huckel[4] in 1898. This investigator concedes the specificity, inoculability and immunizing properties of the lesions, but does not regard the bodies described as parasites. After a painstaking study he regards the inclusions as specific degenerative changes in the epithelial cells induced by the vaccine and variolous virus.

Councilman,[5] basing his opinion upon his own extended investigations and those of his associates, regards the *cytoryctes variolæ* as the parasite causing smallpox. The bodies occur within the epithelial cells, within the nuclei and free. They do not occur as isolated structures, but follow each other in a cycle corresponding with the cycle of development of living things. In the different cases the same forms are found at the same period of the disease. The bodies increase rapidly in the lesions, and the lesions increase in extent by continuous infection of adjoining cells.

Councilman states that in vaccinia the same forms of parasites are found as in the cytoplasmic cycle of variola. The intranuclear forms, however, have never been seen in vaccinia. There is some difference in vaccinia in the size and in the rapidity of development of the parasites in the different tissues and in the different animals. "The differences are not greater than will be shown by the same flowers in different gardens."

Councilman and Tyzzer both discuss the dissenting opinions as to the parasitic nature of Guarnieri's bodies. Their derivation from leukocytes, red blood cells, extruded nuclear material, and specific cell degeneration is considered and the negative evidence presented.

Councilman says that bodies simulating those which occur in smallpox may be found as accidental products in a number of conditions. In these there is no complexity of structure, such as is found in most of the smallpox bodies, and there is no sequence representing growth development. The morphological products of cytoplasmic degenera-

[1] La Riforma Med., 1894.
[2] Ann. Pasteur Inst., April, 1897.
[3] Vaccination, 1899, p. 123.
[4] Die Vaccine Körperchen, Beitr. z. path. Anat., vol. **25**, Supplement.
[5] Jour. Med. Res., February, 1904.

tion do not simulate the parasites. The cells in which the youngest forms of parasites are found have morphologically normal nuclei and cytoplasm. Moreover, the earliest degeneration in smallpox is found in the more superficial cells of the epidermis, while the parasites are in the lower. The intranuclear parasites are less apt to be confused with accidental products than are the cytoplasmic. They are found in nuclei in which there is no change in the chromatin and they stand in no relation to the chromatin.

The Guarnieri bodies, therefore, have commanded most attention in relation to the etiology of smallpox, and Calkins[1] has described what he believes to be their life cycle, but their exact relationship to the disease is still undecided and in the meantime nothing really definite is known on the subject.

IMMUNITY IN SMALLPOX.

Smallpox occurs spontaneously only in man, although some of the lower animals may be infected experimentally. Instances of natural immunity to this disease are rare; not infrequently, however, persons are encountered who are apparently resistant or immune to repeated cowpox vaccination, and in some instances these are known to have escaped smallpox infection. In the great majority of such instances of resistance to first vaccination failure is due to the use of a faulty virus rather than to actual natural immunity.

Unvaccinated human beings of all ages and both sexes are extremely susceptible to smallpox. The mortality among the aborigines and negroes is especially high. The child *in utero* may be infected by placental transmission of the virus providing the mother has smallpox.

One attack of smallpox usually protects for life, but second and even third attacks are known to have occurred. After recovery from smallpox immunity principles may be found in the blood. Attempts toward inducing passive immunization of animals against cowpox and smallpox by means of the injection of blood from vaccinated animals have been occasionally successful; likewise in a few experiments the viruses of cowpox and smallpox have been successfully neutralized or destroyed *in vitro* through contact with the blood serum of vaccinated animals and human beings recovered from smallpox, as first shown by Sternberg,[2] in 1892.

Complement-fixation in Vaccinia and Smallpox.—In 1906 Jobling[3] reported positive complement-fixation reactions, using as antigen a suspension of finely ground calf vaccine pulp and the sera of vaccinated calves. In 1909 Beintker[4] reported indifferent results in which he used as antigen a salt solution extract of calf lymph and the sera of vaccinated rabbits and calves as well as the sera of persons suffering

[1] Jour. Med. Res., February, 1904.
[2] Trans. Assn. Am. Phys., 1892, p. 98; Centralbl. f. Bakteriol., 1896, **29**, 857.
[3] Jour. Exper. Med., 1906, **8**, 707.
[4] Centralbl. f, Bakteriol., 1909, **48**, 500.

with smallpox. In the same year Sugai,[1] using as antigens salt solution extracts of the contents of smallpox pustules and calf lymph, reported positive reactions with the sera of 6 smallpox patients and 5 persons who had been vaccinated with calf lymph. He found no evidence of agglutination in an extract of calf virus material by these era. Dalm[2] reported positive results with the sera of 10 persons suffering with smallpox and an antigen of calf lymph; he also used watery extracts of the liver and spleen of a two-year-old child who had succumbed to smallpox, but with negative or indifferent results; this investigator also found agglutination of calf lymph by the sera of smallpox patients to be weak or entirely absent. Kryloff,[3] using a salt solution extract of variola matter, reported positive reactions in variola and varioloid and considered the complement-fixation test as possessing diagnostic value. Aqueous and alcoholic extracts of variolous scabs and the liver and spleen of persons dead of variola as well as salt solution extracts of calf lymph yielded negative or weaker reactions. Bermbach[4] tested the sera of animals before and after vaccination and the sera of vaccinated and revaccinated persons with a salt solution extract of lymph and reported generally positive reactions. Xylander[5] tested 31 sera of persons before and after vaccination with an alcoholic extract of lymph in an effort to study the specificity of the Wassermann reaction in syphilis. Of these the sera of 8 reacted weakly positive with the lymph antigens, and 7 of these reacted in the same manner with the alcoholic extract of heart; after vaccination 18 reacted weakly positive with the lymph antigen and these included the sera of the same 7 persons who reacted weakly positive with the alcoholic heart antigen prior to vaccination. Teisser and Gastinell,[6] using as antigen a salt solution extract of calf lymph, reported positive reactions with the sera of 39 persons suffering with variola, the reactions becoming positive about the tenth day of the disease and remaining so for at least thirty days; more prolonged observations were not made. Positive reactions were also reported with the sera of vaccinated rabbits, the reactions becoming positive about the seventh day after vaccination. Recently Klein[7] has also reported favorable results with the complement-fixation test in variola, especially with antigens prepared of the contents of the vesicles and pustules of variola, and believes the test to possess practical diagnostic value. Konschegg[8] has also reported positive reactions in variola with salt solution extracts of the contents of variolous lesions. Chang and Chen,[9] however, in a study employing the serums of 50 smallpox patients and antigens of variolous lymph, observed negative reactions with 45 serums.

Kolmer[10] prepared antigens of the contents of vesicles and pustules and the scabs of vaccinia and vaccine pulp from calves and from the

[1] Centralbl. f. Bakteriol., 1909, **49**, 650.
[2] Ibid., 1911, **51**, 136.
[3] Ibid., **60**, 651.
[4] Ibid., 1909, **48**, 618.
[5] Ibid., **51**, 290.
[6] Ibid., 1912–1913, ref., **55**, 555.
[7] München. med. Wchnschr., 1914, **61**, 2270.
[8] Ibid., 1915, **62**, 4.
[9] Ztschr. f. Immunitäts., 1921, **31**, 18.
[10] Jour. Immunol., 1916, **1**, 59.

contents of vesicles and pustules and scabs of smallpox patients. With these complement-fixation reactions were conducted with homologous antigens and sera and the immunological relationship between vaccinia and variola studied by crossing the antigens and sera in complement-fixation experiments; the results were as follows:

1. The sera of rabbits inoculated with cowpox virus yielded positive complement-fixation reactions with salt solution antigens of cowpox and smallpox viruses in seven to eight days after vaccination.

2. The antibody of cowpox virus in the sera of vaccinated animals showed a distinct and close biological relationship to the antigen of variola in complement-fixation experiments.

3. Of 13 persons vaccinated with cowpox virus from seven day to ten years previously, and whose sera yielded negative Wassermann reactions, positive reactions with salt solution antigens of cowpox virus were observed with 4, or 22 per cent. The sera of 1 of these 4 persons yielded positive reactions (vaccinated eight, twenty-one, twenty-two and twenty-four days previously) with cowpox virus, reacted positively with a salt solution antigen of variolous material. The sera of unvaccinated persons reacted negatively with all antigens.

4. Of 17 persons suffering with mild smallpox, the sera of 9, or about 60 per cent, yielded positive complement-fixation reactions with salt solution antigens of variolous and cowpox viruses. While the degree of complement absorption was relatively weak in all instances, the reactions were generally stronger with the variolous antigens than with the cowpox antigens.

5. Alcoholic extracts of variolous and cowpox viruses possessed little or no antigenic sensitiveness.

6. These complement-fixation reactions have demonstrated the close biological relationship between the antibodies of vaccinia and variola; it is probable that complement-fixation reactions with salt solution antigens of the contents of smallpox lesions or fresh cowpox virus will prove of some value in the diagnosis of smallpox.

Immunological Relationship Between Smallpox and Alastrim.—A review of the literature indicates the identity of the mild variola-like disease known as "alastrim" which has prevailed in the West Indies, Brazil, Africa and Australia with the mild smallpox of the United States and Canada. This relationship has also been demonstrated recently by Leake and Force[1] in cross-immunity tests between alastrim and mild smallpox and between alastrim and vaccine virus.

THE DIAGNOSIS OF SMALLPOX.

The Paul Test in the Diagnosis of Smallpox.—The virus of smallpox maintains its infectivity for long periods of time and is capable of producing typical lesions when applied to the cornea of the rabbit.

[1] Hyg. Lab. Bull., 1927, No. 189, p. 29.

Paul[1] has taken advantage of these facts in developing a practical diagnostic test for the disease. The corneal lesions may be identified about forty hours after inoculation, but if not the eyes are removed and placed in an alcohol bath when the lesions are readily identified and particularly when sectioned for microscopic examination.

The test has also been used by Gins and Friedman[2] for the detection of virus in the naso-pharynx of recovered cases of smallpox before quarantine is removed since, according to their findings, the virus may persist in the naso-pharynx for several weeks.

Scott and Simon[3] regard the test as a most valuable method for the diagnosis of smallpox and its differentiation from varicella and other diseases resembling smallpox. They state that a negative result probably always warrants a negative diagnosis, if satisfactory material is available for the examination. As in other laboratory tests, experience with the technique is required, but it would appear worth while for municipal laboratories to be equipped for conducting it. The material for the test is sent to the laboratory dried on clean glass slides and in one instance retained infectivity for the rabbit cornea at ice-box temperature for three hundred and eighty-seven days. Of course, precautions must be taken in the transport of specimens to prevent the inoculation of susceptible human beings and laboratory workers conducting the test should be vaccinated. Loewenthal[4] states that he has observed 23 per cent false negative reactions, but states that a few false positives may have been due to avoidable errors.

A few vesicles or pustules are cleansed with alcohol, wiped dry with sterile cotton and opened with a sterile needle or a small lancet. The exuding vesicular or pustular material is mounted on clean slides in the form of *thick drops*. These are allowed to become air-dry and the specimens may then be wrapped in paper and sent to the laboratory in a suitable container. If the pustular stage has passed a number of scales should be lifted from their beds and sent as such. Care should be taken, however, to secure only round, brown scales with a smooth surface. Yellow irregular crusts with fissured surfaces are usually devoid of virus. Serum from papules is not suitable for examination.

Both eyes of a rabbit are anesthetized with a few drops of a 5 per cent solution of cocaine hydrochloride, and then *delicately* scarified with a fine needle, making four or five horizontal and as many vertical scratches, about 1 mm. apart. A loopful of as heavy an emulsion in saline as can be prepared from the material submitted for examination is then gently rubbed over the scarified surface of one eye. The other cornea serves for purposes of control. The animal is kept by itself in a cage, which is sterilized after use. In about forty-eight hours the eye is

[1] Centralbl. f. Bakteriol., orig., 1915, **75**, 523; 1918, **80**, 361. Deutsch. med. Wchnschr., 1917, No. 29, p. 900; 1917, No. 45, p. 1415.
[2] Deutsch. med. Wchnschr., 1916, No. 1118; 1917, No. 37.
[3] Am. Jour. Hyg., 1923, **3**, 401; Jour. Lab. and Clin. Med., 1925, **10**, 562.
[4] Schweiz. med. Wchnschr., 1925, **55**, 429.

examined, removed, placed in bichloride alcohol and reëxamined for the typical lesions of smallpox.

The detection of smallpox in its pustular stage, particularly in well-marked eruptions, is a facile matter even for the merest tyro in medicine. The picture of a profuse pustular variola can scarcely be mistaken for anything else.

It is especially the mild and modified forms of smallpox that present difficulties in diagnosis. The degree of protection in varioloid may be so great that the eruption may consist of but a few papules, or, indeed, the eruption may be absent altogether, constituting a variola sine exanthemate. The diagnosis in such cases would, of course, present perplexities. It is a matter of considerable importance to ascertain whether variola is prevailing in a community, and whether the patient has been exposed to the infection. The inability to obtain satisfactory testimony as to direct exposure should not be allowed to influence the diagnosis, as infection may take place in the most subtle manner and from unsuspected sources.

The degree to which the patient is protected by vaccination or previous attack of smallpox should always be investigated. The presence of a comparatively recent vaccine scar, or pits of a former attack, would constitute strong presumptive evidence against the existence of smallpox in the individual.

As variola is communicable during the initial stage, an early diagnosis often becomes highly important. If, in a given case, it be found that the patient was seized with a chill or had repeated rigors, followed by a sudden rise of temperature to an unusually high degree, and that there is epigastric tenderness, irritability of the stomach, and severe pain in the lumbar region, variola should be strongly suspected. If, together with these symptoms, there can be obtained a history of exposure to the variolous infection, the diagnosis becomes comparatively easy. But in many cases of variola, and particularly of varioloid, the initial symptoms are so indefinite that a diagnosis is quite impossible until the characteristic eruption appears.

There is no one symptom of smallpox which is so characteristic that it may not be absent. In making a diagnosis the prevalence of an epidemic, the vaccine condition of the patient, the history of the disease, and the symptoms as they present themselves should all be carefully considered.

The initial illness of smallpox may be confounded with influenza, typhus or typhoid fever, meningitis and acute gastritis.

Differential Diagnosis.—La Grippe.—In severe cases of la grippe the disease may be ushered in with intense headache, fever, delirium and violent pain in the back and limbs, symptoms which strongly suggest smallpox. The differential diagnosis between these affections would be impossible before the appearance of the eruption. Knowledge of the prevalence of the one or the other disease would be an aid in the diagnosis.

Typhus Fever.—The early symptoms of typhus fever may be quite indistinguishable from those of the initial stage of smallpox. The appearance of the eruption will usually establish the diagnosis. The eruption of typhus is at first macular, and is seldom present on the face, while that of the smallpox is papular and begins usually upon the forehead.

Meningitis.—In both meningitis and variola, violent headache, delirium and coma may develop. In the cerebrospinal form purpuric symptoms are not uncommon, but retraction of the head and rigidity of the muscles of the neck, so commonly seen in this affection, are seldom encountered in smallpox.

Typhoid Fever.—It is surprising how many patients sent into the Philadelphia Hospital for Contagious Diseases with smallpox were treated during the initial stage of the disease, as cases of typhoid fever. This is, perhaps, owing to the former frequency of the latter disease in Philadelphia. In an ordinary case of enteric fever the insidious onset and the gradual rise of temperature will distinguish it from variola, in which the onset is sudden with chilly sensations, fever often reaching 104° or 105° F. and commonly with severe headache, backache and vomiting.

Acute Gastritis.—The error of confounding the early manifestations of variola with acute gastritis is at times made in cases in which the initial illness is characterized by severe and persistent vomiting, with pain in the pit of the stomach. Attention to the associated symptoms and the history of the case should enable one to arrive at a correct diagnosis.

The mistaking of the early lumbar pain for *lumbago* could only result from an insufficient examination of the patient. Lumbago is not attended with fever and the other constitutional disturbances that characterize the initial illness of smallpox.

Measles.—Measles may be confounded both with the morbilliform prodromal rash and with the beginning true eruption of variola. The prodromal rash is non-elevated, irregular in distribution, with predilection for the trunk and extremities, of evanescent duration (twenty-four to forty-eight hours) and usually appears upon the second day of the initial illness in those about to develop the eruption of varioloid. In measles catarrhal symptoms are present and the eruption is later in making its appearance.

That measles may bear a close resemblance to smallpox is evidenced by the fact that in epidemics of variola cases of measles are not infrequently sent to the smallpox hospitals under erroneous diagnosis. It is the confluent form of variola which, in the early eruptive stage, resembles measles most, for in this type of the disease the face is often considerably suffused. Standing at the foot of the patient's bed in such cases it is frequently impossible, from the appearance of the eruption on the face alone, to distinguish between the two diseases. Some cases of measles are accompanied by more papulation than others,

particularly on the face and wrists, and these are the cases that most strikingly simulate smallpox.

The diagnosis can, in the vast majority of cases, be determined by attention to the following points:

The constitutional symptoms preceding the eruption in smallpox are usually more severe (temperature, 104° to 105° F.) and are commonly, though not always, accompanied by pronounced backache. The temperature, moreover, falls a few days after the appearance of the eruption, while the fever in measles at this time continues high. The catarrhal symptoms affecting the eyes and the respiratory passages and the buccal eruption, which are so constant in measles, are absent in smallpox, at least during the prodromal stage. Close inspection of the mouth in smallpox may reveal the presence upon the soft palate of rounded, glistening, pin-head-sized, reddish elevations, but these differ considerably from the bluish spots on the buccal mucous membrane in measles. The eruption in measles consists of large maculopapules which are soft and velvety to the touch, while the papules of smallpox are smaller and have a firm and shotty feel. The sweep of an experienced hand over the skin will often suffice to differentiate the two diseases. Where there is doubt, twenty-four hours' delay will dispel all uncertainty, for by this time the eruption of measles will have become flatter and more diffuse, and the papules of smallpox firmer and more distinctly elevated.

Scarlet Fever.—The peculiar distribution and fleeting character of the scarlatiniform prodromal rash will enable one to distinguish it from scarlet fever.

Scarlet fever may, however, be closely simulated by that form of hemorrhagic smallpox in which the entire cutaneous surface becomes the seat of a diffuse, dusky-red rash, especially well marked in the crural triangle. This form of purpura variolosa is, however, usually preceded by excruciating backache. If the patient be watched for a short time a few ill-defined vesicles will usually make their appearance. The development of hemorrhages would not in itself be conclusive, as these might occur in hemorrhagic scarlet fever, except that hemorrhage beneath the conjunctiva would rather indicate the existence of smallpox. The early occurrence of sore throat would point toward the scarlatinal nature of the disease.

Chickenpox.—The differential diagnosis between varicella and variola is discussed in the chapter on chickenpox.

Syphilis.—It may at first seem strange that syphilis and smallpox should ever be confounded. Upon reflection, however, it will be seen that the two diseases have many phenomena in common. They are both infectious diseases due to the invasion of the blood with a microorganism. Each has a period of incubation, at the end of which there develop certain general manifestations accompanied by an exanthem and an enanthem. The resemblance may be still further accentuated by the fact that the variolaform syphilide is not rarely associated with and even preceded by fever and general aches and pains.

It is particularly the pustular syphiloderm which is apt to be confounded with smallpox. The eruption at times may appear rather suddenly and pass through the stages of papule, vesicle and pustule in a surprisingly brief period of time. The lesions may be quite firm to the touch and in other respects closely simulate those seen in smallpox.

In syphilis one can frequently obtain: 1. *A history of infection* and a description of the initial lesion. Indeed, the chancre or its remains may still be detected. Not uncommonly there are present associated evidences of syphilis, such as flat condylomata, ulceration of syphilis, such as flat condylomata, ulceration of the tonsils, alopecia, glandular enlargement, etc. The variolaform syphilide may develop after the disappearance of one of the earlier syphilitic eruptions.

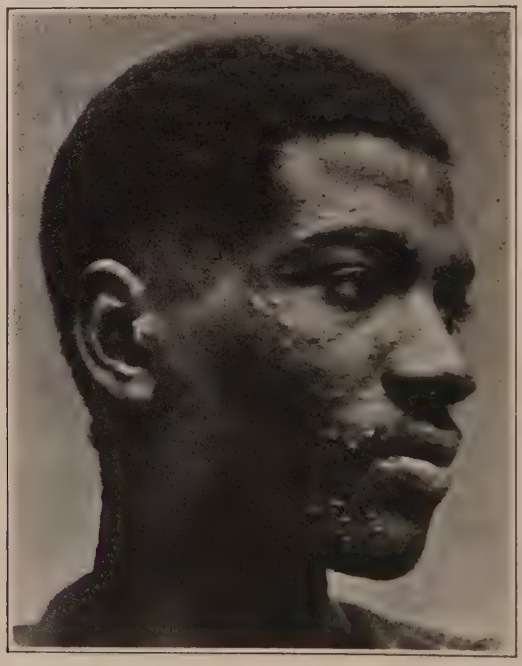
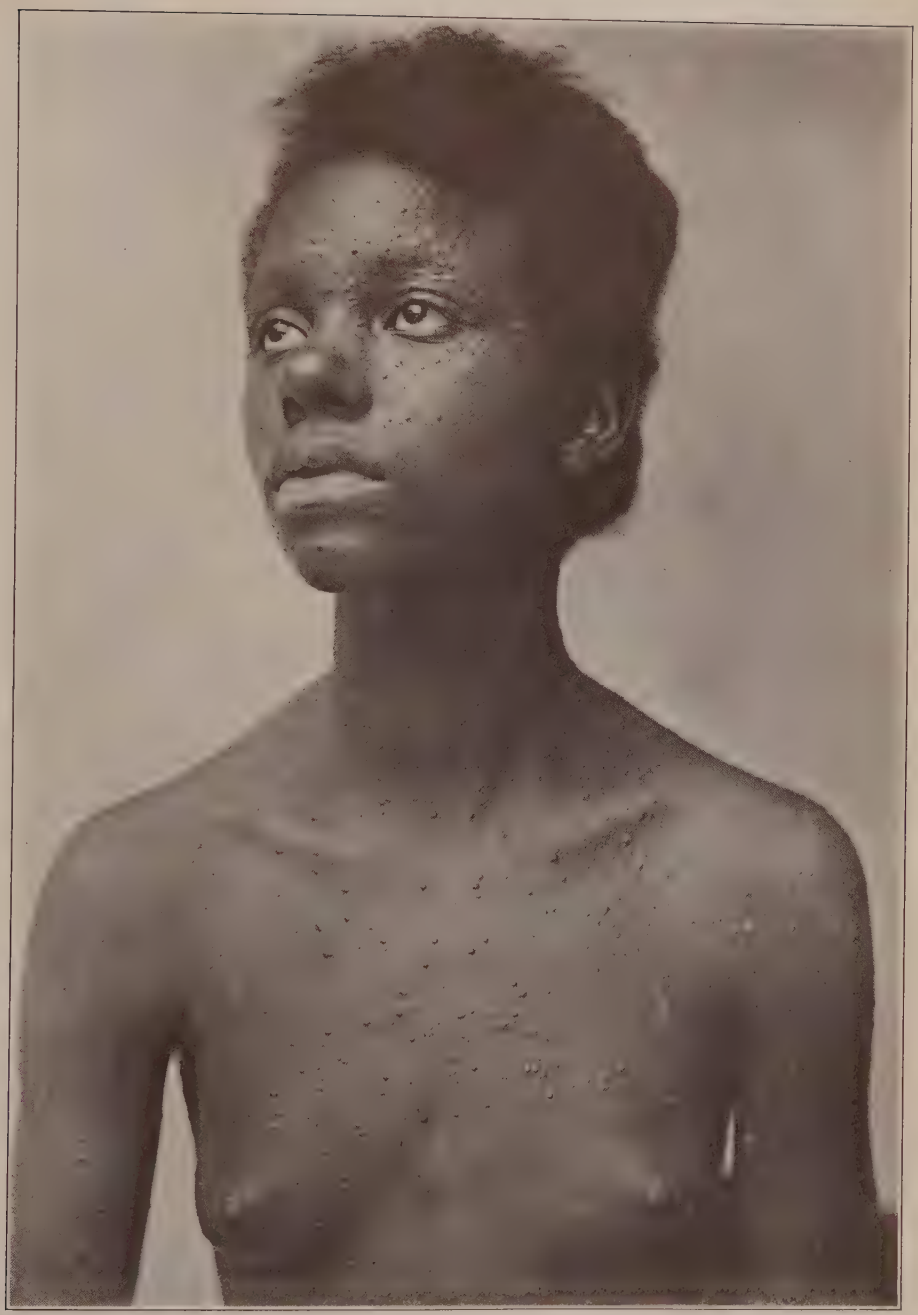


Fig. 72.—Syphilis resembling smallpox.

2. *The onset of the two diseases* is, as a rule, quite different. The syphilitic subject will usually give a history of having felt weak and debilitated for some weeks. If fever precedes the eruption it is ordinarily not very high and is not accompanied by severe prostration. When the eruption appears the patient usually calls upon the physician at his office or at the hospital. We do not note that sudden illness which precedes unmodified smallpox. In the latter disease, two or three days before the efflorescence appears, the patient experiences a chill followed by a rise of temperature, often to 103°, 104° or 105° F. There

PLATE XI



Pustular Syphilide Bearing a Considerable Resemblance to Smallpox.

are severe headache, backache, vomiting or nausea, vertigo, general pains and severe prostration. The patient, instead of calling upon the physician, sends for him.

It must be remembered, however, that in varioloid the initial symptoms may be mild or absent. On the other hand, in rare cases, syphilis may present an initial illness which suggests that of smallpox.

3. *The development of the eruption* in smallpox is rather sudden. Ordinarily in twenty-four to forty-eight hours the full complement of lesions has appeared. In syphilis the eruption may continue to come out for quite a number of days in successive crops. It must be admitted, however that in modified smallpox three or four days may sometimes elapse before the complete appearance of the exanthem.

4. *The distribution* of the variolaform syphilide may be identical with that observed in smallpox. Frequently, however, variations may be noted. The pustular syphilide may involve the trunk more copiously than the face; this would be exceedingly rare in well-marked smallpox. The dorsal surface of the wrists and hands are nearly always involved in smallpox, but may escape entirely in syphilis. The palms of the hands and soles of the feet are always involved in severe smallpox; in moderate eruptions they nearly always present some lesions, and in varioloid they may or may not escape completely. *The pustular syphilide, on the contrary, attacks the palmar and plantar surfaces, the vermilion border of the lips and the glans penis, rarely if ever.*

5. *The character of the eruption* in syphilis and smallpox may, in the beginning, be so nearly identical as to make a diagnosis from the eruption alone quite impossible. It will be noted, however, that the efflorescence of smallpox presents a much greater uniformity in the character and development of the lesions over the body than does syphilis. Syphilis is characterized by an essentially multiform eruption; it is not uncommon to find small pustules, large pustules and papules interspersed, and these in varying stages of evolution and involution.

The vesicles and pustules of syphilis are usually conical and involve merely the summits of the elevations; they never become full and globular, and fill the entire lesion as do those of smallpox. Beneath the syphilitic crusts considerable ulceration not uncommonly occurs; according as this is slight or severe there will be seen, upon detachment of the crusts, a small reddish-brown pigmented stain or an excavated ulcer. The latter heals with the production of a depressed scar.

6. *The course* of the syphilitic eruption is relatively chronic compared with that of smallpox. The lesions of variola undergo a striking change in a few days. The syphilitic efflorescence is indolent, and presents, as a rule, no decided alteration of appearance within this period of time, By the sixth or seventh day in smallpox the lesions develop into those large, full, round, hemispherical pustules which are so characteristic of the disease.

7. In syphilis spirochetes may be found and the Wassermann reaction is positive.

8. Finally, to the physician who has seen much of smallpox, there is a something in the picture, an impression given by the *ensemble*, which, while not definable in language, is, nevertheless, of subtle aid in the diagnosis.

Roseola Vaccinosa.—Vaccination with animal virus sometimes causes an erythematous or rubeoloid rash, known as roseola vaccinosa, to appear from the eighth to the twelfth day of the vaccine disease. We have occasionally known this rash to have been mistaken for the eruption of variola, especially during epidemic visitations of the disease. The distinguishing features are that it accompanies vaccinia, that it is not preceded by a very high temperature and that it consists of macules rather than papules.

FIG. 73.—Pustulo-bullous eruption, resulting from the ingestion of large doses of bromides, sent into the hospital as a case of smallpox.

Acne.—Mild cases of varioloid exhibiting but few papulo-pustules about the face may bear a close resemblance to acne. The history of exposure, the existence of an initial stage, and the progressive evolution of the lesions will speak for the variolous nature of the eruption, while the presence of blackheads, a history of previous outbreaks in the individual, and the absence of preceding illness will decide in favor of acne.

Drug Eruptions.—Drug eruptions, particularly those resulting from the ingestion of the iodides and bromides, may simulate the exanthem of smallpox. The history and absence of an invasive stage will usually suffice to make the diagnosis clear.

Impetigo Contagiosa.—A confounding of smallpox with impetigo contagiosa can come only from a misunderstanding of the nature of the latter disease, which is a purely local dermatosis resulting from inoculation of the skin with certain pyogenic microörganisms. The eruption is usually limited to the face and neck, although occasionally a few lesions may be present upon the hands. The trunk and lower extremi-

ties are, save in rare cases, free of eruption. The lesions do not ordinarly exceed a dozen in number. They are usually discrete, thin-roofed vesicles and blebs, which rapidly become turbid and dry into yellowish flat crusts. These are cast off, leaving faint, reddish stains. The vesico-pustules are extremely superficial and flat, and appear to be on the skin rather than in it. The disease being local in character, there is, as a rule, neither fever nor any other systemic disturbance. The eruption is both contagious and autoinoculable, the infection occurring through direct or intermediate contact. The disease is more common in children than in adults.

FIG. 74.—Varioliform eruption in a patient with ulcerative endocarditis. Illness fatal. Resemblance to smallpox strong.

Glanders.—Glanders in an early stage may be mistaken for smallpox. The febrile symptoms are not unlike those of variola, and the subepidermic abscesses when small feel like hard infiltrations in the skin. In this disease, however, there are, in addition, deep-seated abscesses, infiltration of the areolar tissue, rapid ulceration and at times gangrene. The disease is rare and the patients are usually stablemen.

Eczema.—Severe crusted eczemas of the face may bear a rough resemblance to confluent smallpox during the desiccative stage. We have known physicians experienced in smallpox to make this error through a hasty and superficial examination of the patient. Inspection of the trunk and extremities will make the diagnosis clear.

During epidemics the anticipatory attitude of the physician's mind will often lead him to suspect and diagnose as variola diseases which bear only a superficial or remote resemblance to it. Thus, patients

with febrile herpes, herpes zoster, erythema multiforme and other skin diseases have at such times been sent to smallpox hospitals as cases of variola. Contrariwise, in the absence of an epidemic mild cases of smallpox are very likely to be overlooked.

Whenever the diagnosis between smallpox and a disease simulating it is in doubt, observation of the progress of the eruption for a period of twenty-four to thirty-six hours will usually make clear the nature of the disease.

THE PROGNOSIS OF SMALLPOX.

Since the introduction of vaccination the presence or absence of a typical vaccine scar on a patient is an important factor in the question of prognosis in smallpox. Formerly, smallpox was not only more common, but uniformly far more fatal, and therefore much more dreaded than at the present time.

During the last century but few diseases claimed a greater number of victims than variola, but at the present time, especially in countries where vaccination is carefully and systematically practised, the proportion of deaths from this malady is not greater than 0.7 per cent of the entire mortality, and where revaccination at the proper age is also enforced this proportion is even much less. In the prevaccination period one-tenth of all the children born died from smallpox; now the mortality from that disease among young children where vaccination is compulsory is almost *nil*.

Age.—The age of the patient is of the greatest importance in considering the prognosis of smallpox. It is comparatively rare for an infant under one year of age to survive an attack of unmodified smallpox. So also at the other extreme of life the death-rate is excessively high. In children of from one to five years of age the disease is also very fatal, but among those of from five to fifteen years the chances of recovery are rather better than in adult life.

SMALLPOX PATIENTS TREATED IN THE PHILADELPHIA HOSPITAL FOR CONTAGIOUS DISEASES, SHOWING MORTALITY ACCORDING TO AGE.

Series I.

Age.	Cases.	Died.	Percentage.
Under 1 year	60	37	61.66
1 to 15 years	530	187	35.28
15 to 25 "	1362	402	29.51
25 to 45 "	1215	365	30.04
47 years and upward	227	88	38.77
Total	3394	1079	31.79

Series II.

(Similar table with somewhat different age classification.)

Age.	Cases.	Died.	Percentage.
Under 1 year	57	29	50.87
1 to 5 years	159	50	31.45
5 to 10 "	130	20	15.38
10 to 15 "	66	8	12.12
15 to 25 "	371	55	14.82
25 years and upward	1096	172	15.69
Total	1879	334	17.80

The above tables give the smallpox mortality according to age, and include both the vaccinated and the unvaccinated cases. All of the patients under one year of age were unvaccinated except a few who were vaccinated after infection, *i. e.*, during the incubation period.

In Series I are included the statistics of the large and malignant epidemic of 1871–1872 and of a subsequent severe epidemic, while in Series II are included the statistics of the much milder epidemic of 1901–1902.

Race.—When smallpox prevails among aboriginal tribes the mortality is extremely high. It is commonly stated that the death-rate of variola among negroes is much higher than among whites. This statement has scarcely been borne out by our experience. Negroes are extremely negligent as regards vaccination, and the number of unvaccinated colored people received in smallpox hospitals is apt to relatively exceed the number of unvaccinated whites.

Sex.—Sex influences prognosis to little or no extent.

Among women the mortality is somewhat increased on account of their liability to suffer from metrorrhagia, or, when pregnant, from miscarriage or premature delivery. The occurrence of either of these accidents or the presence of the parturient state strongly predisposes the patient to the hemorrhagic form of the disease. The mortality in men is, on the other hand, considerably increased by intemperance. Drunkards or constant imbibers seem particularly prone to suffer from hemorrhagic smallpox.

Unmodified smallpox is an exceedingly fatal disease, the death-rate varying in different epidemics from 15 to 60 per cent. The epidemic which swept over this and other countries in the years 1870 to 1872 was everywhere characterized by unusual malignancy, and the mortality among the unvaccinated cases was in some places as high as 64 per cent. The following table shows the mortality-rate among vaccinated and unvaccinated cases treated in the Philadelphia Hospital for Contagious Diseases during the three largest epidemics experienced since its existence:

Mortality-rate of Vaccinated and Unvaccinated Cases in Different Epidemics.

		Cases.	Deaths.	Percentage.
1871–1872.	Unvaccinated	697	449	64.41
	Vaccinated	1629	276	16.94
	Total	2326	725	30.74
1881–1885.	Unvaccinated	447	252	56.37
	Vaccinated	551	81	14.70
	Total	998	333	33.36
1901–1904.	Unvaccinated	1943	636	32.73
	Vaccinated	1844	124	6.72
	Total	3787	760	20.06

It will thus be seen that different epidemics vary very greatly in malignancy. In 1901–1904 the mortality-rate among the unvaccinated was just one-half that observed in 1871–1872, and almost one-half less than the death-rate in 1881.

Type of Disease.—In considering the prognosis in individual cases various circumstances are to be taken into account. The *type of the disease* and the *extent and depth of the eruption* are among the most important factors. The hemorrhagic form of smallpox is frightfully fatal. Indeed, it may be laid down as a rule almost without exception that recovery never takes place from the graver types of this disease. Of 152 cases of hemorrhagic smallpox observed during the epidemic of 1871–1872, 146 died. The 6 cases that recovered belonged to the milder variety of this type; 1 had slight bloody vomit and the other 5 exhibited an eruption which on some parts of the body was purplish, while a number of vesicles contained a dark-blue spot in the center, showing that blood was exuded into the vesicles.

The next and most fatal form of smallpox is the confluent variety. When it is comprehended that in such cases there may be forty thousand or more pustules present, the reason for the high death-rate is apparent. Of 211 cases of confluent smallpox accurately observed during the epidemic of 1871–1872, 168 died, showing a mortality-rate of 79.61 per cent.

Semi-confluent cases are correspondingly less fatal than the confluent, while in cases with discrete eruptions the mortality falls to a comparatively low level.

Thus it will be seen that the prognosis in any particular case is influenced to an enormous extent by the character of the eruption. In varioloid or smallpox so modified by vaccination, inoculation or previous attack that the secondary fever is slight or absent, the mortality is almost *nil*, as will be seen from the appended table:

Variola and Varioloid Treated in the Philadelphia Hospital for Contagious Diseases.

	Cases.	Deaths.	Percentage.
Variola	4156	1906	45.93
Varioloid	3048	31	1.01
Total	7204	1937	26.89

The fatalities in varioloid result, as a rule, from some complicating condition. It must be remembered that attacks in adult patients who were vaccinated in infancy and showed no appreciable protection are classed under the head of variola.

The stage of the disease at which death occurs in smallpox will depend somewhat upon the character of the attack. Patients suffering from hemorrhagic variola usually succumb on the fourth, fifth or sixth day of the eruption. Considering all types of the disease the largest number of fatalities occur during the second week of the erup-

tion and particularly upon the ninth, tenth and eleventh days. Of 1019 fatal cases of smallpox, 575, or 56.42 per cent, died during the second week, and 347, or 34.05 per cent, of these expired on the ninth, tenth and eleventh days. Basing the assertion upon these figures, it may be stated that over one-third of the fatalities occur upon the critical days mentioned, and over one-half of the deaths during the second week.

We have occasionally observed death to take place as late as five or six weeks after the onset of the disease, but in these cases the unfavorable termination has been brought about by some complicating affection.

Vaccinal Condition.—The vaccinal condition of the individual is a most potent factor in influencing the course of the variolous disease. The degree of protection conferred by the vaccine process can be, in most cases, approximately estimated by the character of the vaccine cicatrix. Every now and then we encounter patients with good vaccination scars from an infantile vaccination, in whom the protection against smallpox has been almost completely lost; on the other hand, we may see patients with poor scars who still enjoy considerable protection; but these may be looked upon as exceptions to the general rule.

The existence, therefore, of good cicatrices in a patient who is attacked with smallpox may be regarded as of favorable prognostic import.

Of 8893 cases of smallpox treated at the Philadelphia Hospital for Contagious Diseases, 2335 presented good scars; of this number, 152 died, constituting a mortality-rate of 6.5 per cent; 1105 patients with fair scars were treated, of whom 135 died, showing a death-rate of 12.21 per cent; 1524 cases were admitted with poor scars, of whom 345 died, giving a death-rate of 22.64 per cent; 3687 unvaccinated cases were admitted, of whom 1542 died, giving a mortality-rate of 41.82 per cent. Thus it is seen that the danger of attacks of smallpox can be measured with a considerable degree of accuracy by the vaccinal condition of the patient.

VACCINAL CONDITION AND MORTALITY-RATE.

	Admitted.	Died.	Percentage.
Vaccinated in infancy:			
Good scars	2335	152	6.50
Fair scars	1105	135	12.21
Poor scars	1524	345	22.64
Postvaccinal cases	4964	632	12.53
Unvaccinated cases	3687	1542	41.82
Unclassified cases	242	45	18.18
Total	8892	2219	24 95

There is no reliable symptom during the initial stage to indicate the gravity of the attack. Not infrequently the mildest eruption of varioloid is preceded by a very severe febrile stage. If, however, the initial

stage be very mild it is safe to prognosticate a moderate eruption. Severe lumbar pains may be present both in modified and unmodified smallpox, yet if they be extremely severe there would be some reason to anticipate a hemorrhagic form of the disease. Inasmuch as the initial morbilliform exanthem (*roseola variolosa*) is most often seen in varioloid, we would regard the presence of this rash as an indication that the true eruption will be of modified form. When the rash is of the scarlatiniform type the ensuing eruption may be moderate or severe; when, however, the prodromal rash is purpuric it is a symptom of evil portent, preceding as it does the hemorrhagic form of the disease. There are, however, exceptions to this last statement; we have occasionally seen erythemato-purpuric prodromal rashes in persons who have made perfectly good recoveries.

It has been already stated that the quantity and character of the eruption are accurate guides as to the gravity of the disease. The condition of the mucous membrane of the pharynx, larynx and trachea should be regarded as only second in importance to the skin lesions in estimating the degree of danger in variola. If these parts become severely implicated by the variolous process, giving rise to a diphtheritic condition of the fauces, dysphagia, difficulty of respiration or edema of the glottis, the case should be viewed with grave apprehension. Even hoarseness at the early period of the maturative stage should be looked upon with suspicion.

Favorable Symptoms.—As has been stated, mild initial manifestations and the occurrence of a roseolous rash are favorable, inasmuch as they precede, as a rule, mild forms of the disease. Even in profuse eruptions, if the pustules become prominent and acuminate well, and are accompanied by considerable swelling, and if those on the extremities are surrounded by a pinkish areola, and the patient takes nourishment freely, there is good ground for hope. At a more advanced period of the disease, if the state of the nervous system be tranquil and the patient passes quiet nights, has a contented disposition and entertains a confident hope of recovery, the probability of a favorable termination of the disease is greatly increased, even though the eruption be severely confluent.

Unfavorable Symptoms.—Among the symptoms which indicate the approach of a hemorrhagic attack are: Excruciating backache during the initial stage, a petechial prodromal rash in the axilla and groins, subconjunctival ecchymoses and hemorrhages from the various mucous membranes, a claret-colored areola about the lesions upon the extremities and a bluish or lead-colored discoloration of the centers of the vesicles. The prognosis in a case presenting such symptoms would be almost hopeless.

An extensive degree of confluence on all parts of the body renders the prognosis extremely grave. It is an unfavorable sign in confluent cases if the pustules on the face be flat, milky-white in color and pasty, and if there be absence of swelling. It is also ominous to see here and

there on the face vesicles desiccating prematurely and producing flat, brownish scabs.

During the early period of maturation the patient's condition should be regarded as extremely critical if the progress of the eruption be suddenly arrested and the swelling of the face and hands subside, leaving the skin between the pustules pale; if the pustules themselves shrink and collapse; if the pulse be rapid, dicrotic or feeble; if the delirium and restlessness increase; or if nourishment be refused or taken very reluctantly.

Valuable information may often be gained by observing the nervous symptoms, especially at an advanced period of the disease. Great restlessness, insomnia, despondency, constant moaning and grinding of teeth in children are unfavorable symptoms. Violent and protracted delirium, convulsions or coma usually preclude all hope of recovery.

Even after the patient has passed safely through the perils of the regular stages of variola, his life may again be placed in jeopardy by certain complications. Fortunately, those which are most frequent—furuncles and abscesses—rarely lead to a fatal issue. The occurrence of pneumonia, pleuritis with effusion, erysipelas or abortion should be viewed with deep concern. But the most fatal of the complications liable to arise are suppuration within the joints, pyemia and empyema. Gangrene of the scrotum and glossitis variolosa arising earlier in the course of the disease usually portend a fatal outcome.

THE TREATMENT OF SMALLPOX.

The treatment of smallpox may be considered in its relationship (1) to the patient himself, and (2) to the community at large. The latter aspect of the subject concerns the prophylaxis or preventive treatment of the disease. This may be conveniently classified under the following captions—notification, isolation, surveillance or quarantine, disinfection and vaccination.

Prophylaxis.—Notification.—It is important in the interests of public health that the existence of a case of smallpox should be promptly made known to the proper health authorities. It is usually the duty of the physician in attendance to transmit this intelligence. Every practitioner of medicine should feel himself called upon to aid and sustain the sanitary authorities in their efforts to prevent or stamp out a pestilential disease and should willingly comply with any arrangements whose object is the attainment of so desirable an end.

Most large communities have enacted laws making compulsory the notification of smallpox and other pestilential diseases, under pain of fine or imprisonment. It is only through a knowledge of the distribution and extent of smallpox in an infected district that the health authorities are enabled to intelligently and efficiently inaugurate measures toward its suppression.

Isolation.—It is of paramount importance, when smallpox appears in a community, to prevent the dissemination of infection; to this end the isolation of the patient—the source of the infection—becomes essential. This can only be accomplished with any degree of certainty by having the sick removed to a well-organized hospital. General hospitals and other public institutions cannot, with justice to the other patients or inmates, harbor and treat those suffering from smallpox. Even the caring for such patients in isolated pavilions in general hospitals is open to the objection of multiplying the foci of contagion in the city or town. It follows, therefore, that every city and large town should be provided, either temporarily or permanently, with a special institution for the treatment of this disease in the event of its outbreak. It should be located in a healthful district, sufficiently removed from the thickly settled portions of the city to preclude the possibility of transmitting the contagion to inhabited domiciles, but not so remote as to interfere with its accessibility. It is also of importance that such institutions should be constructed in a modern manner, with a view to making the unfortunate patients as comfortable as possible.

Of course, a special hospital of this character should be managed under strict quarantine regulations. No person, however well protected, should be allowed to visit a patient in the institution except under extreme circumstances, and then only after every possible precaution shall have been taken to prevent his carrying away the infection. The nurses and attendants should not be allowed to leave the hospital, nor come in contact with other persons, until they have had an antiseptic bath and have changed their infected clothing. In providing nurses and other employees for the hospital it need not be required that they shall have had smallpox, but they should invariably be vaccinated or revaccinated before entering upon duty. When delay is possible it is wise to await the result of such vaccination before the individual is brought into the infected atmosphere. The hospital should be supplied with closed ambulances for the transportation of patients. Private or public vehicles should never be used for this purpose. Indeed, this is regarded as so important a matter that in some large cities in this country the use of any kind of public conveyance for carrying persons afflicted with smallpox is prohibited by law, and its infringement is made punishable by fine.

Lest infection be spread by the ambulance itself, it should be disinfected and provided with clean bedding, blankets, etc., every time it is used. In order that the public may know the character of the disease that it conveys, it should bear the name of the hospital to which it belongs.

If the smallpox patient is to be treated at home every possible effort should be made to seclude him from all persons, excepting only such as are required to act as nurses, and they should be protected by recent vaccination. In selecting the apartment for the patient, a room most

completely separated from all other parts of the house is to be preferred. If this is not practicable, which is usually the case in the ordinary city residence, the uppermost room of the house should be preferred. It should be well ventilated, and, if possible, have an open fireplace in which fire should be kept constantly burning. All unnecessary articles of furniture, such as drapery, upholstery, carpets, etc., should be removed. Every precaution in regard to cleanliness and disinfection of bedding, clothing and everything in use in the room should be exercised, so that the danger of spreading the infection shall be reduced to the minimum. A sheet wrung out in a strong solution of carbolic acid, Labarraque's liquid or some other disinfectant, and suspended across the doorway, may aid in preventing the infection from being disseminated to other parts of the house. The spaces around doors that are not in use, which communicate with parts of the house to be protected, should be sealed by pasting strips of wrapping paper over them.

Surveillance or Quarantine.—When smallpox appears in a house the question arises, What shall be done with the exposed but well members, of the household? If the patient is treated at home the other inmates as well as the sufferer should be quarantined. For if removed to another locality, save to a quarantine station or hospital, the disease might subsequently appear there, and a new center of infection be thus established. To depend upon people voluntarily to curtail their personal liberty for the public good would be confiding too much, at the present time, in human benevolence and public spirit. Therefore the best results will be obtained, when the patient is retained at home, by stationing reliable guards about the house to enforce detention of the exposed inmates and also all other necessary precautionary measures.

On the other hand, when the patient is removed to the hospital it is, in our judgment, not necessary to enforce the above-mentioned restrictions. Indeed, we are of the belief that the object desired is often defeated in large cities by a routine quarantine of the inmates of houses from which smallpox patients have been removed. To make such a quarantine effective the individuals should be detained for a period of eighteen days, the outside limits of the stage of incubation. Segregation of the inmates of the household for so long a period works a great personal hardship and prompts them in many instances to escape before the quarantine is placed upon the house. We have known persons frequently to flee from houses where there existed an individual suspected of having smallpox, but in whom the diagnosis had not been definitely made. The settling of these exposed persons in different parts of the same city and in other cities results in the outbreak of the disease in these various localities. Thus, instead of limiting the infection rigid quarantine laws may favor its dissemination. Furthermore, unpopular restrictive measures tend to provoke evasion of the law and concealment of the existence of the disease.

When the patient is removed to the hospital we would advise immediate vaccination of the exposed individuals. To avoid, as far as

possible failures through imperfect virus or technique, three or four insertions with different virus had better be made. At the same time there should be thorough disinfection of the infected articles and apartments. After this has been accomplished the exposed individuals might resume their freedom. They should, however, be kept under medical surveillance, and should be daily visited by a physician who should watch for any symptoms of variola. Such inspection should be continued for sixteen days from the onset of the disease in the original patient, at the end of which time the suspected individuals, if well, may be exempted from further surveillance. During his visits the physician can determine whether the vaccinations are "taking," and if not, the procedure can be repeated, thus giving the patient a still further chance of protection if vaccinal susceptibility exists.

The above plan is based upon the assumption that smallpox is not contagious during the period of incubation, and this view is in accord with the belief held by practically all authorities on the subject. Until active symptoms manifest themselves the exposed individual is not a menace to the health of the community, and it is unnecessary and injudicious to restrict his liberty during this period. Furthermore, a large experience has demonstrated to us that under a system such as outlined, a *much larger percentage of exposed individuals will submit to vaccination and a correspondingly increased number of patients will consent to be removed to the hospital*, for only those who comply with this advice will be exempted from quarantine.

Apart from these considerations, the system of routine quarantine during epidemic prevalence of smallpox will be found to involve the expenditure of large sums of money.

The quarantining of exposed persons may be practicable and wise in dealing with sporadic cases of smallpox or with the first cases in a community, for under such circumstances extraordinary precautions are justified in an endeavor to limit the outbreak of the disease to the original patients.

Another means of restricting the spread of smallpox is to apprise the public of the particular locality in which the disease exists, so that no one may unknowingly approach within infecting distance of the place. The plan adopted in most cities of *placarding* the infected house with a large and conspicuous poster is believed by many to serve the best purpose.

Disinfection.—Disinfection is a highly important prophylactic measure. The infection of smallpox is not only imparted to the atmosphere surrounding the patient, but to all articles which have been used by him or have been near him. It clings to these articles for a variable length of time, and they are, therefore, not infrequently the media by which the infection is conveyed to others. Disinfection consists in the complete destruction of the infecting agent of the disease. Fresh air and sunlight are Nature's disinfectants; when infected articles are freely exposed to the atmosphere and rays of the sun for some time the

infecting principle becomes less and less active and finally disappears. Therefore, the house, especially the room, occupied by the patient should be freely though cautiously ventilated.

Chemical substances, however, furnish the more speedy and reliable disinfectants, and it is upon such that we mainly depend for the destruction of the disease germs. Some agent of this nature should be brought directly in contact with all the excrementitious matter from the patient, and with everything that has been used by him or has been near him during the progress of the disease. All discharges, not excepting those from the mouth and nose, should be received into a vessel containing some such disinfectant as chloride of lime, carbolic acid or bichloride of mercury. Under no circumstances should the excreta be allowed to flow into the sewer or be cast away without first having undergone disinfection. In country districts, where disinfectants may not be readily obtained, the discharges should be deeply buried in the ground in a locality where there is no danger of contaminating the water supply. Every handkerchief, towel and article of bedding and clothing used by the patient should be steeped for some time before leaving the room in a solution of 1 to 1000 bichloride of mercury or 4 fluidounces of carbolic acid to the gallon of water, and afterward boiled by themselves for one-half hour or longer in plain water; all small articles, such as bits of linen, sponge, absorbent cotton and the like should be burned immediately; all utensils used for eating and drinking should be purified by boiling water; in short, nothing should be allowed to leave the room without having first been subjected to some form of disinfection.

The attendants should not be more numerous than the necessities of the case require. They should be carefully instructed in regard to the importance of cleanliness, disinfection and isolation. Not only should they be instructed to exclude from the sick-room all persons not having authority to enter, but also all domestic animals, such as the dog and cat, as they are exceedingly liable to serve as conveyers of the infection.

The clothing of the attendants should be of such material as can be readily boiled and washed, and it should be frequently changed and subjected to this process. No attendant while engaged with the case should come in contact with other persons. On leaving, either temporarily or permanently, a bath should first be taken, using freely carbolic acid soap, and the hair should be washed with a solution of mercuric chloride. No clothing that has at any time been in the infected atmosphere should be worn or carried away from the premises, unless it has first been disinfected.

Physicians should also exercise care lest they may be the means of communicating the infection. When called upon to attend a case of smallpox the physician should not remain in the infected atmosphere longer than is necessary to make a proper examination; the prescription may be written and advice given in another apartment. After

each visit he should carefully wash his hands, face and hair; his hands especially should be washed in some disinfecting solution. He should then expose himself for a considerable time in the open air before visiting another patient.

The physician should wear in the sick-chamber a long mackintosh or a linen duster buttoned up to the chin and a cap to cover the hair, and these garments should be kept hanging in the open air in the intervals of his visits. In hospitals where there are many patients to be examined, and where he is required to spend considerable time in the wards, nothing short of a change of his entire outer clothing before leaving the institution should be considered. It is also of importance for the physician to cover his shoes with rubbers, so that no variolous crusts which may be upon the floor will be carried out of the infected house.

The isolation of a smallpox patient should be continued until all the scabs are removed. The time necessary to effect their separation varies greatly in different cases. In severe confluent forms of the disease a month or more will be required, while in extremely mild and abortive cases of varioloid the skin may be entirely smooth in a week or ten days. Upon the palms and soles the inspissated pocks remain embedded for a long time and require mechanical removal in order to avoid a long and tedious waiting for spontaneous exfoliation. Even after removal of the variolous crusts the patient should not be allowed to associate with the public until he has had one or more antiseptic baths. Perhaps the most reliable antiseptic bath that can be given is one containing corrosive sublimate. The safest way one may proceed in the use of such a bath is by simply sponging the body and carefully wetting the hair with the solution (1 to 2000) and then have the patient freely bathed in plain water with the use of carbolic acid soap, or the patient may take a full bath in a tub containing a 1 to 10,000 or 1 to 20,000 solution of mercuric chloride. A 5 per cent solution of Labarraque's liquid also makes a very reliable disinfecting bath. After this he should put on clothing which has not been exposed to the infection, or, if exposed, has been disinfected, and he may then safely mingle with the public.

Inasmuch as the body of a person who has died of smallpox is capable of imparting the infection, some precautions should be observed in regard to it. For instance, the body should be thoroughly wet with a solution of corrosive sublimate (1 to 1000) or with a solution of chloride of lime in proportion of 6 ounces of the drug to a gallon of water, or with some other equally powerful disinfectant; besides, it should be wrapped in a sheet saturated with one of these solutions and buried at once. The preferable method of disposing of the dead from this disease is by cremation; but this method is yet perhaps too strongly opposed by public sentiment to be practicable. It is not advisable to transport the corpse a long distance or from one city to another for burial, but if this be really necessary it should first be placed in a

metallic coffin hermetically sealed. In its burial it should be put at least 6 feet under ground and should not be disinterred unless absolutely necessary, and then only under sanitary supervision. The vehicle used for conveying the body to the grave should afterward be disinfected. It is, perhaps unnecessary to say that the funeral should by no means be public.

After the sick chamber has been vacated, either by recovery or death of the patient, every article it contains of no great value should be immediately burned. Everything else which will not be injured by the ordinary operation of the laundry may be safely and cheaply disinfected by immersion in boiling water for one-half hour. It should be remembered, however, that the water must be maintained at the boiling-point for that length of time. But if it is impracticable to subject such articles at once to the boiling process, they should be immersed for about four hours in some reliable disinfecting solution—such as mercuric chloride in the proportion of 1 to 2000, or carbolic acid 1 to 50—and subsequently boiled.

The sick-room should be thoroughly disinfected with formaldehyde gas. The room should then remain closed from twelve to twenty-four hours, afterward opened, throughly ventilated, and all surfaces, including the furniture, washed with a disinfecting solution (carbolic acid 1 to 50, or mercuric chloride 1 to 1000); afterward the floor and other woodwork should be thoroughly scrubbed with soap and water. The wall paper , if there be any, should be well moistened with the carbolic acid solution and scraped off and burned. In addition to all these precautions it is advisable to have the room remain unoccupied for three or four weeks, during which time it should be well aired.

For disinfection of outer clothing, carpets, bedding and all articles which cannot be boiled, there is nothing superior to steam under pressure. The germs of smallpox will certainly perish if exposed for one-half hour to this agent at a temperature of 230° F. There are, however, certain articles which would be injured by moist heat, and for the disinfection of these dry heat may be substituted. In this case a temperature of at least 230° F. continued for two hours will be required. Formaldehyde, however, could be used instead of dry heat.

Vaccination.—Of all of the measures employed to prevent the spread of smallpox, none is so important and efficacious as vaccination.

In the absence of a statutory law requiring the vaccination of all persons very much can be done in the way of enforcing the measure by restricting the privileges of the unvaccinated. For instance, satisfactory evidence of successful vaccination should be required of every child before admission into public and private schools and institutions for the care of children; no unvaccinated person should be allowed to serve as a soldier in the army or navy or in the state militia; and no unvaccinated immigrant should be allowed to land until vaccination has been performed.

In view, therefore, of the great importance of this prophylactic

measure, it becomes the duty of all municipal and state authorities to provide gratuitous vaccination for the poor, and, indeed, for all helpless children of careless or improvident parents, no matter to what class of society they belong.

Whenever a case of smallpox occurs in a family the physician's first duty is to vaccinate promptly all members of the family who have never been vaccinated, and revaccinate all others without regard to the character of their previous vaccination. It is a good plan to vaccinate on several successive days those who have never been previously subjected to this procedure, in order to increase the probability of obtaining a successful result. If this be done and the patient sent to the hospital the disease may be prevented from spreading.

Care of Patient.—In order to consider in detail the treatment of smallpox it seems most convenient to divide the disease into its various stages, as follows: (1) The stage of incubation; (2) the initial stage; (3) the eruptive stage; (4) the stage of suppuration; (5) the stage of retrogression, or stadium exsiccationis.

1. **The Stage of Incubation.**—The interval between the reception of the infecting agent of smallpox into the blood and the earlier manifestations of the disease is usually unattended by symptoms. There is no doubt, however, that certain unknown processes take place during this period. It is very important to know whether anything can be done at this time to arrest or change these processes so as to prevent or modify the approaching disease. Drugs, of course, are powerless for this purpose. Is vaccination at this period capable of exerting any such influence?

We have had very frequent opportunities of observing that vaccination during the invasive or initial stage of smallpox is utterly valueless, and also that it is equally useless when performed only three or four days prior to the earlier invasive symptoms. A vaccine vesicle resulting from a vaccination performed at the period just mentioned, and the variolous pustules, will, it is true, develop side by side without the one exerting any influence whatever over the other. Curschmann's experience seems to warrant the inference that at no time within the incubation period of smallpox can vaccination be used with advantage against the approaching disease. If such is his experience it certainly differs very greatly from our own. We have in numerous instances seen smallpox very markedly modified by vaccination performed at this period, and not infrequently have seen it prevented absolutely. In order that protection shall be complete it is necessary that the insertion of the vaccine lymph should be made almost immediately after the reception of the contagium; but if made at a somewhat later date a modifying effect may still be obtained. No part of the incubation period should be considered too late to make use of this remedy, since this period is sometimes prolonged beyond its usual limits, in which case a late vaccination may prove of value.

It is our opinion that vaccinia does not begin to exert its prophy-

lactic power until the areola commences to form around the vesicle. At this time the mild febrile reaction, which was regarded by Jenner as a *sine qua non* in true vaccinia, becomes apparent. If this stage of the vesicle be reached before the patient shows any symptoms of smallpox, the disease may be entirely prevented; if not reached until after the febrile symptoms appear, but before the eruption occurs, it may modify the attack. Now, it is well known that in typical vaccinia the areola appears about the seventh or eighth day from the date of insertion of the lymph, and is at its height on the ninth or tenth day; and it is equally well known that the incubation period of variola is, in the majority of cases, of ten or eleven days' duration, and that the eruption does not appear until about three days later. This renders quite obvious the fact that vaccination, practised shortly after variolous

FIG. 75.—Smallpox and vaccinia running a coincident course, the vaccination having been performed about three days before the appearance of the variolous eruption. Photographed on eighth day of eruption.

infection has occurred, has an opportunity in point of time to exert more or less prophylactic influence against the incubating disease. While no inflexible rule can be laid down, it may be said in a general way that if vaccination be practised on the first or second day after the reception of the infection into the system, the protection may be perfect; and if employed between this date and the fifth day it may be partial. But we would emphasize the fact that after infection has occurred every day that is allowed to pass before resorting to vaccination is so much valuable time lost.

In endeavoring to confer protection during the incubation stage of smallpox the quality of the vaccine lymph employed has a great deal to do with the success. Nothing is of more vital importance at this period of the disease than that the vaccine virus employed should be fresh and active. The difference between success and failure in pro-

ducing vaccinia after exposure often means to the patient the difference between life and death.

In order to ensure success *it is advisable to employ virus, when possible, from more than one source*. It is desirable at this time to guard as far as possible not only against failure, but also against a vaccine disease of slow progress. A tardy vesicle, or one that is slow in making its appearance and late in arriving at maturity, gives no assurance of safety.

In making the fullest effort to ensure success it is advisable to vaccinate the exposed person each day for two or three days in succession. It is far better that the individual should have an excessively sore arm than suffer from an unmodified attack of smallpox.

We have observed the effects of vaccination during the period of incubation in 370 cases. The vaccinations were all primary and were performed at various periods of this stage from immediately after the reception of the infection until two days before the appearance of the eruption.

In support of the statement already made, namely, that the vaccine disease does not begin to exert its prophylactic power until the vesicle has reached the stage at which the areola appears, we present the following table:

PATIENTS VACCINATED AFTER EXPOSURE.

	Cases.	Deaths.	Percentages.
Vaccinated seven days or less before the variolous eruption	106	39	38.79
Vaccinated more than seven days before the variolous eruption	264	39	14.77
Total	370	78	26.78

From these figures it is conclusively proven that the earlier the vaccination is performed during the period of incubation the greater is the chance of the disease being favorably modified.

Some of the deaths occurring in patients vaccinated more than seven days before the eruption may be attributed to a too tardy development of the vaccine lesion. Most of the patients were vaccinated with bovine lymph, and it is known that this lymph, particularly when used in the form of dry points, is slower in its effect than humanized virus or glycerinated lymph.

Forty-seven persons vaccinated for the first time by us after exposure to smallpox were perfectly protected against the disease. As these individuals were all under observation in the hospital, where they came in the closest possible contact with smallpox patients, there can be no question that the contagium was present in sufficient quantity to ensure immediate infection.

2. **The Initial Stage.**—The initial stage of smallpox comprises the period between the earliest manifestation of the disease and the appearance of the eruption, and has a duration usually of about three

days. All attempts to stay the disease, or even modify its course, have proved unavailing, and we can do nothing more at this stage than treat special symptoms as they arise.

FIG. 76.—Smallpox in a child vaccinated after exposure: Favorable modification of the smallpox eruption.

Every effort should be directed toward keeping the patient as comfortable as possible, and experience shows that a bedroom well ventilated and having a temperature of from 65° to 70° F. is best suited for this purpose. The ordinary febrifuge mixtures, such as liquor ammoniæ acetatis, liquor potassi citratis, tinctura aconiti, etc., may be given in suitable doses and at stated intervals. We are in the habit of using the following formula:

℞—Spirit. ether. nitrosi,
Syrup. limonis . . . . . āā f℥iv
Liquor. ammonii acetatis . . . . . f℥v.—M.
Sig.—Give 2 to 4 fluidrams every two hours in a little ice-water.

If there is irritability of the stomach the effervescing citrate of potassium may be preferable. It sometimes happens that the stomach is very irritable, especially in children; in this case lime water, subnitrate of bismuth, aromatic spirit of ammonia, a little chloroform water, of any other drug or agent known to be of service in this condition, may be used. The swallowing of small pieces of ice will often give relief when everything else fails. When the skin is hot and dry and the temperature high, frequent sponging with cool water is serviceable. Severe headache may call for the application of cold water, iced compresses or an ice-bag to the head. These need not be feared on account of the popular superstition that they tend to suppress the eruption, for such is not the case.

Nervous symptoms, such as insomnia, delirium and convulsions, are often prominent features of the disease and demand appropriate treatment. Some of the bromide salts or chloral, given either separately or in combination, will usually succeed in subduing these symptoms. For the convulsions of children there is perhaps nothing more effective than chloral, given either by the mouth or rectum. When given by the mouth it should be well diluted, since it is very irritating to the throat, which is liable to become implicated in the variolous process quite early. Warm baths are also very useful. There is another nervous symptom commonly present at this stage of smallpox, and that is pain in the back. This is sometimes so distressing as to call for measures of relief. When the stomach is retentive Dover's powder may be given, or some one of the analgesic coal-tar products, now so frequently used to relieve pain. Sometimes there is much restlessness and general irritability; in such cases we have found a little morphine, combined with the febrifuge prescription above referred to, to act most happily.

The common practice of applying mustard to the back for the relief of pain or to the epigastrium to lessen gastric irritability cannot be too strongly condemned, since the variolous eruption always appears in much greater abundance on irritated surfaces. Wherever there is an ulcer, a wound or an excoriated condition of the skin there the pustules are sure to be found in dense clusters. We have frequently seen the eruption intensely confluent over regions of the skin where a mustard plaster had been applied during the initial stage of the disease. Some have thought that the eruption might in this way be diverted from the face to other localities, but we are convinced that it is not diminished anywhere else by reason of its confluence on these parts through the action of a sinapism; rather is it increased to that extent.

The digestion at this stage is not vigorous; hence the diet should be light and easily assimilable. There is nothing more suitable than animal broths and milk. The best beverages are cold water and iced lemonade. Acidulated drinks seem to be particularly grateful to the palate. Gentle cathartics may, of course, be administered whenever indicated.

3. **The Eruptive Stage.**—The eruptive stage may be said to comprise a period beginning with the first appearance of the eruption and ending when pustulation has fully occurred. The duration of this stage in variola vera is usually seven or eight days, but in modified smallpox it is shortened in proportion to the degree of modification.

The treatment during the eruptive stage of smallpox should be directed toward alleviation of the subjective symptoms and the correction of special symptoms as they arise. Usually it is not until the eruption appears that the disease is recognized and the degree of severity prognosticated. If the case promises to be at all severe all flannel undergarments should be at once removed, and the hair cut close, so that the head may be kept cool, cleanliness enforced, the risk of cellular inflammation of the scalp diminished and a better opportu-

nity afforded for the employment of cold applications should delirium or more urgent brain symptoms arise.

The febrile symptoms which usher in the disease now usually remit, but increase again as the eruption progresses. For this condition the remedies already mentioned may be continued. It sometimes happens in a depressed condition of the system, particularly in children, that the extremities and even the surface of the body are cool, and that the eruption is too slow in making its appearance. In such cases the application of heat and the administration of hot stimulating drinks, such as hot toddy, may be of service. This condition in children is apt to be associated with convulsions, in which case there is nothing better than a warm bath followed by an envelopment in warm blankets. Should the convulsions continue, however, chloral, by either mouth or rectum, is quite sure to give relief. We repeat here the caution not to fail to dilute the chloral freely, for the throat is now so much involved in the variolous process that an irritating draught may give rise to croupous symptoms, or even acute edema of the glottis.

Treatment of the Throat.—As the eruption progresses, not only the fauces, but the soft and hard palate, the buccal mucous membrane, the larynx and sometimes the trachea also become more or less involved in the process, and this is often the source of difficult and painful deglutition. This condition requires the use of mouth washes and gargles, such, for example, as those containing chlorate of potash, boric acid, glycerole of tannin, tincture of myrrh, etc. We have found the milder demulcent fluids made from flaxseed, gum arabic, or slippery-elm bark particularly grateful. Of these none is more relished by the patient than flaxseed tea, sweetened with white sugar and acidulated with lemon juice. Careful and frequent cleansing of the mouth affords considerable relief. This may be done by the nurse covering her index finger with a piece of soft linen, dipping it into a solution of boric acid with glycerin added, and then thoroughly and carefully cleansing the entire buccal cavity.

During the epidemic of 1901–1904 we found orthoform, in 1-gr. lozenges, useful in lessening the distressing soreness of the throat and mouth. In severe cases, however, where the throat was covered with lesions we were obliged to use a cocaine (1 per cent) spray in order to lessen the pain in swallowing, and thus enable patients to partake of sufficient nourishment. We have never noted untoward results from the employment of cocaine in this form.

The pain in the throat and difficulty in swallowing are often benefited by having the patient hold in his mouth small pieces of ice and allowing these to dissolve slowly. Where there is much glandular swelling the application of the ice-bag externally will be found useful. Some patients, however, will prefer the use of poultices or hot fomentations. When there is much fetor some antiseptic, such as carbolic acid or permanganate of potash, may be added to the mouth wash or gargle. We have found dilute chlorine water to answer a good purpose.

Variolous glossitis is best treated by mild antiseptic mouth washes and the use of pellets of ice. Should acute edema of the glottis or of the aryepiglottic folds occur, an emetic may be given if the patient is not too weak, or local scarification may be practised. When suffocation threatens tracheotomy offers the best if not the only chance of recovery.

Treatment of Nervous Symptoms.—Toward the latter part of the eruptive stage of variola persistent insomnia and delirium often occur. When this condition of the patient is attended by a flushed face and bounding pulse an ice-bag to the head and a brisk cathartic may be of service. Tartar emetic and sulphate of morphine, in doses of from $\frac{1}{8}$ to $\frac{1}{2}$ gr. each, will often produce sleep and quiet the delirium. Morphine is a most valuable drug in controlling restlessness and inducing sleep during the pustular stage of smallpox. To accomplish this end it is sometimes necessary to administer $\frac{1}{2}$ or $\frac{3}{4}$ gr. of the drug in twenty-four hours. However, it is usually well borne and the patients are almost always benefited by its use. Large doses of bromide of potassium, or chloral freely diluted, may be given and repeated if necessary. Some care, however, must be taken not to push these remedies too far, lest the patient lapse into coma or a state of profound prostration.

Occasionally the delirium is of that violent kind which the older writers styled "delirium ferox." This is accompanied by a wild expression of the countenance, and such a strong tendency to escape from the attendant or to self-destruction, that too much care cannot be exercised for the safety of both the nurse and the patient. We have known strong and muscular patients, while in this state of mind, to knock the nurse down, jump out of the window and run to some secluded place, where they would cunningly secrete themselves. We have also known patients to attempt suicide in various ways while the nurse was temporarily absent. The necessities of the case, therefore, often require the use of some artificial means of restraint. For instance, a wide band of stout webbing or canvas may be placed loosely over the patient's chest and secured to each side of the bed. Similar bands of the same material may be fastened to each wrist and ankle, or leather wristlets and anklets may be used, the former being secured to the sides of the bed and the latter to the foot of the bed, allowing, however, a little motion of the limbs, so that the patient shall not be subjected to painful restraint. In the meantime every effort should be continued to quiet the delirium, and when the patient refuses to swallow the drugs and nourishment should be administered by the rectum.

It is deemed appropriate to speak of the treatment of hemorrhagic smallpox under this head, for the peculiar manifestations of that type of the disease become strikingly apparent during the eruptive stage; moreover, it is rare for a well-marked case to live beyond the limits of the vesicular stage. Treatment is of little avail in this phase of variola. Transfusion and hypodermoclysis with saline solution have been tried, but have not given very encouraging results.

This type of the disease in varioloid is not quite so significant of danger as in variola. We have seen a few hemorrhagic cases of varioloid, in which the hemorrhage from internal organs was not very profuse or protracted, although the purpuric spots were well marked, recover under the free use of iron and stimulants. In these cases nourishment was freely taken, prostration was at no time profound, and, as the patients passed favorably through the eruptive stage of the disease, the petechiæ gradually disappeared and convalescence became established.

The most appropriate *diet* during the eruptive stage of variola is a liquid or soft diet. It should be easy of digestion and very nutritious, for the patient has yet to pass through a severe ordeal, in which his power of endurance will be tested to the utmost. Such articles as animal broths, milk and eggs may be freely given. Bread may be added to the broths or to the milk, or it may be given in the form of milk toast. In varioloid the appetite during this stage is often unaffected; such patients require but little treatment and may be allowed almost perfect freedom in choice of diet.

4. **Stage of Suppuration.**—The indications for treatment during this stage are to mitigate the fever, to disinfect the exudation from the skin, to relieve the dangerous throat symptoms and to resist by every possible means the tendency to death from exhaustion. If the patient's life can be prolonged through this stage, his chances for recovery increase with each succeeding day.

The febrile reaction which had abated considerably when the eruption first appeared, now increases to a notable degree, sometimes reaching a greater elevation than existed during the initial stage. In variola confluens the temperature at this period of the disease usually ranges from 103° to 106° F. Various drugs and other means have been employed for the purpose of reducing the intense heat of the body, but not one of them has given results entirely satisfactory. Quinine has been recommended, but in order to exert its antithermic properties it must be given in doses of 10 gr., repeated every one-half hour or hour until 40 gr. have been taken. This usually produces effects so unpleasant that we seldom give it in antipyretic doses. We use it, however, quite freely as a supportive and also on account of its favorable action in preventing septicemia. Some one of the antipyretics of the coal-tar series may occasionally be found useful. There is no doubt about the power of either antipyrin, acetanilide or phenacetin to reduce temperature, but we do not feel sure that the use of these drugs in all cases is unattended with risk. However, when used carefully and in selected cases we do not think the risk is very great. We have found the administration of phenacetin in $2\frac{1}{2}$- or 5-gr. doses, when the temperature is high, to lessen the fever by 1° or 2° F., without producing any unpleasant effects.

Baths.—Cool immersion baths, which have been recommended so highly in Germany for reducing high temperature in typhoid fever,

have not met with anything like the same favor, even in that country, in the treatment of variola. Apart from the difficulty of getting a patient in the pustular stage in and out of the tub, it is found that they do not afford much relief. The use of cold compresses and of cold sponging are more easy of application and are very often serviceable. We have seen patients temporarily benefited in warm weather by covering them with sheets wrung out of cold water, but usually this treatment is not well borne in cold weather.

Continuous warm baths are often of great value in the treatment of smallpox. We have employed the continuous warm bath in smallpox in a limited number of cases and have been most favorably impressed with its therapeutic value. The cases in which it was tried were desperate types of confluent smallpox, and, although we were unable in several of the patients to save their lives, the baths conduced much to their comfort. A bath of 95° F. seemed to be capable of reducing a temperature of 104° to 100° F. or thereabouts and of maintaining the temperature at about this level. With the reduction of the fever, the pulse decreased in frequency and delirium was replaced by sleep. We kept one young man with a most severe type of confluent smallpox in a continuous bath for five days. On removing him from the tub to the bed at the end of this time his temperature immediately rose from 100° to 103° F. Life was prolonged in this case, but the systemic poisoning was too profound to permit of recovery.

Apart from the antipyretic influence of the continuous warm bath, it tends to macerate the pustules, hastens the discharge of their contents, and thus lessens the liability to secondary pyogenic infections of the skin. We have found the ordinary ward tub with an adjustable cradle attachment admirably adapted for continuous baths. In winter hot water must be frequently added to keep the temperature up to the desired degree. When the temperature of the water falls below 92° or 90° F. the patient will usually complain of chilliness. The continuous bath treatment requires the services of a special attendant night and day. We believe it is one of our most important therapeutic measures in smallpox.

Supportive Measures.—During the suppurative stage of smallpox the vital forces of the patient are put to the severest possible test. The prostrating effect of the septic absorption from the innumerable pustules must be necessarily very great. Watson has estimated that the quantity of pus in the skin amounts to quarts; that this estimate is quite accurate is evidenced by the fact that we found the amount in a case of confluent smallpox, by actual computation, to be 5 quarts. So extraordinary a drain upon the system demands that the strength of the patient should be vigorously supported; otherwise, evidence of exhaustion soon becomes apparent.

The first evidence of flagging of the vital powers is often seen in the subsidence of the redness and swelling of the face and hands; the skin becomes pale, the pustules present a shrunken or collapsed appearance

and the pulse grows rapid and feeble. Other symptoms indicative of exhaustion are subsultus tendinum, general tremors, a dry tongue and delirium. These are always indications for the most liberal use of stimulants and nutritious and easily assimilated food. It is wiser, however, not to wait until the vital energies begin to flag before resorting to supporting measures. As the patient approaches the suppurative stage his strength should be preserved by constant reinforcement, so as to enable him to encounter the struggle that is to follow.

It is our practice to commence with stimulants and nutrients at the beginning of the suppurative stage or earlier when deemed necessary. The method of their employment is about as follows: To an adult patient suffering from the confluent variety of the disease we direct that there shall be given in each twenty-four hours not less than 2 quarts of unskimmed milk, 2 to 4 eggs and 6 to 12 ounces of whiskey, the latter being given usually in the form of milk punch. The eggs should be well beaten and taken with the milk (a little salt being added), or they may be given in the form of egg-nog. It is important that the nutriment be given at short intervals, since patients can seldom take a large quantity at one time. It is also important that the stimulants and nutrients should be faithfully continued during the night, for many a prostrated patient has sunk beyond recovery between midnight and morning, for the want of these measures.

In selecting the diet and stimulants, we should, of course, take into consideration the condition of the patient's stomach. If that organ should be weak, or disinclined to receive in sufficient quantity the nutritive material just referred to, or if there should be a great repugnance to milk, as is sometimes the case, such articles as bouillon with eggs, well-prepared beef tea, nutritious broths, and liberal amount of wine should be given instead. As a stimulant for patients in profound prostration, Curschmann recommends the Stokes cognac mixture:

℞—Cognac optimi,
Aquæ destillatæ . . . . . āā f℥xv
Vitelli ovi . . . . . No. 1
Syrupi . . . . . f℥vj.—M.
S.—A tablespoonful every two hours.

We would suggest that this preparation might prove more efficacious if repeated more frequently, or given in larger doses.

In the way of drugs, quinine in tonic doses—2 gr. every three or four hours—is, we think, of service at this stage of the disease. Digitalis seems to be indicated at times to steady the action of the heart, but if there be evidence of collapse or cardiac failure, camphor in oil, intramuscularly, together with strychnine, hypodermically, should be given. Delirium, which is often most prominent during this stage, should be treated in the manner already described. No more medicine should be given than is absolutely necessary, for the *less the stomach is taxed with the ingestion of drugs,* and the more entirely it is given over to

the work of *sustaining the vital forces of the body*, the better will be the chances of recovery.

When the bowels are constipated a mild laxative may be administered, or, what is preferable, a simple enema may be given.

5. **The Stage of Retrogression, or Stadium Exsiccationis.**—The stage of retrogression is characterized by drying of the pustules, lessening of the pain, diminishing of the swelling and redness of the skin and of the involved mucous membrane. The eyes again open, the nasal passages become more patulous, swallowing is less difficult, and the countenance, in favorable cases, assumes a brighter and more hopeful appearance. This stage in unmodified smallpox usually begins from the eleventh to the thirteenth day of eruption, and runs very gradually into the stage of convalescence. In cases somewhat modified it commences a little earlier. During the greater part of this period the same general treatment recommended for the preceding stage should be continued. When, however, the patient shows well-marked indications of improvement the quantity of stimulants may be gradually diminished, and such articles as cornstarch, milk toast, soft-boiled eggs, cup custard and the like may be added to the diet. Quinine and some ferruginous preparation, especially the tincture of the chloride of iron, are particularly valuable at this time.

It will occasionally be found necessary to administer remedies for the relief of the diarrhea which may develop during the desiccative stage. The ordinary drugs employed for this purpose, opium, the astringent tinctures, bismuth, etc., will in the majority of cases succeed in quieting the bowels. Often, however, these remedies require to be given in full doses and frequently repeated.

Edema of the feet and legs is not infrequently seen after severe attacks of smallpox. In such cases there is always great exhaustion and the patient is generally anemic. The latter condition is doubtless the cause of the edema in the majority of cases. In the treatment of these cases iron in some form should be administered, and a roller bandage applied to the feet and legs. If the kidneys be diseased, they should, of course, receive appropriate treatment.

The various complications of smallpox, both medical and surgical, should be treated according to the most approved methods, it being borne in mind, however, that the patient is suffering from an exhausting disease and one that has severely taxed the integrity of the important organs and tissues. During the terminal stages of the disease, tonics, particularly those containing iron, quinine and strychnine, will be found extremely useful. Stimulants, especially in the form of malt liquors, and a liberal and nutritious diet will aid in restoring strength and weight to the convalescent patient.

Red-light Treatment of Smallpox.—A form of red-light treatment of smallpox was employed by John, of Gaddesden, in the fourteenth century, and doubtless before him by Arabian physicians; its object was to excite the skin and cause the elimination of the poisons of the

blood. John, of Gaddesden, though court physician, is said to have been "a very sad knave." Gregory wrote, in 1843: "What think you of a prince of royal blood of England (John, the son of Edward the Second) being treated for smallpox by being put into a bed surrounded with red hangings, covered with red blankets and a red counterpane, gargling his throat with mulberry wine and sucking the red juice of pomegranates? Yet this was the boasted prescription of John, of Gaddesden, who took no small credit to himself for bringing his royal patient safely through the disease." Gregory significantly adds: "Let us then avoid the errors of our ancestors without reproaching them."

Picton,[1] Black,[2] Waters,[3] Barlow[4] and others have employed various methods of excluding the actinic rays of light in treating smallpox.

Some years ago Finsen, of Copenhagen, strongly championed the red-light treatment of smallpox. The treatment is based upon the exclusion from the sick-room of the actinic or chemical rays of light by the use of red-colored screens of one material or another. Finsen, in summing up the cases treated by this method, chiefly by Danish and Norwegian physicians, says that out of a total of 140 to 150 cases of smallpox in 1 case only was the method inefficacious.

In the winter of 1902, Dr. Welch and one of the writers treated 2 cases of variola in a red room specially arranged for the purpose, with absolute negative results in both. One patient died during the suppurative fever and the other was badly scarred.

Dr. Nelson D. Brayton, of Indianapolis, observed 300 patients treated in red-light wards, with results no different from those obtained in daylight wards. In 1904 Ricketts and Byles,[5] of London, treated 13 cases of smallpox in a thoroughly equipped red-light room. They stated: "We cannot agree that the treatment has any of the merits which have been claimed for it." We seriously question the assertion that the exclusion of the actinic rays of light will prevent suppuration and scarring in severe smallpox in unvaccinated individuals.

Besides the drugs mentioned we have administered a few other antiseptic remedies, such as salicylic acid, salicylate of sodium and carbolic acid, but we cannot say that we have seen beneficial results from their use. With xylol, which, according to Zuelzer, coagulates the contents of the pustules and cuts short their development, we have had no experience. Others, however, do not seem to have obtained encouraging results which were claimed for this drug.

Convalescent Serum Treatment of Smallpox.—It would appear from experiments performed by Copeman, Chauveau, Béclere, Chambon, and Ménard and others, that the serum of a previously vaccinated heifer is capable, on introduction into a second animal, of producing a certain degree of immunity against a subsequent vaccination.

Prompted by this result, Béclere employed such a serum in the treat-

[1] Am. Jour. Med. Sci., 1832.
[2] Lancet, June 27, 1867.
[3] Ibid., February 4, 1871.
[4] Ibid., July 1, 1871.
[5] Ibid., July 30, 1904.

ment of a woman suffering from smallpox. He injected the enormous quantity of 1½ liters, and believed that the serum produced a most favorable influence upon the course of the disease. Auché, of Bordeaux, and Landmann, of Frankfort, employed serum from persons who had passed through an attack of variola. The quantity of serum injected was necessarily small and no appreciable results were obtained. In this country the serum treatment has been tried by Kinyoun and by MacElliot, the former claiming a successful result.

Dr. Welch and one of the authors used the serum of vaccinated heifers to a limited extent in the treatment of smallpox without material result.

Vaunted Remedies.—Various internal remedies had from time to time have been praised in the treatment of smallpox. Sulphocarbolate of sodium, sodium thiosulphate, bichloride of mercury, brewer's yeast, salicylate of sodium, carbolic acid, xylol, etc., have been advocated. We have tried most of these with no success whatsoever.

More recently Ducamp, de Claret and Falgairolle[1] employed transfusion of convalescents' blood in 4 cases of smallpox. They claim that both the eruption and the general condition improved. The eruption was accelerated, attenuated and the pitting warded off. One patient with all of the mucous membranes attacked died. In one obese woman the serum had to be given subcutaneously and improvement was comparatively slight. Nevertheless, the authors appear to have been impressed with the value of the method.

While this therapeutic procedure is scientifically logical and is worthy of extensive trial, deductions as to the value of remedies in smallpox must be made with discriminating care. So much depends upon the type of smallpox and the previous vaccinal condition of the patient.

Teissier[2] claims recently to have had considerable success from the use of convalescent serum. The blood is taken from patients between the twenty-fifth and fortieth day of the disease, care being taken to select patients free of tuberculosis and syphilis. The serum is injected intravenously or subcutaneously in doses of 35 to 100 cc. Among 13 cases of very severe smallpox treated by this method 8 recovered. These included an unvaccinated child, a case of genuine hemorrhagic smallpox, 3 cases of confluent smallpox with a hemorrhagic prodromal eruption and 3 other confluent cases.

Local Treatment.—The local use of antiseptics in variola has been favorably reported by various writers. Opening the pustules with an aseptic needle, evacuating their contents and sponging with an antiseptic had been advocated.

Good results are alleged to have followed the use of baths containing *permanganate of potassium*, the salt being added until the water is of a rose-red color. Our experience with permanganate baths has been

[1] Du camp et al, Bull. de la Soc. de sci. méd., 1926, **7**, 324.
[2] Roger, Widal, Teissier: Variole, Nouv. trait. de méd., 1922, **2**, 181.

entirely unsatisfactory. The baths were given daily, and in some cases twice daily, from an early period of the eruption. They did not seem to exert any favorable influence upon the course of the eruption or the disease. Indeed, during the employment of this treatment our mortality was more than 50 per cent.

Looking back over the literature of the subject we find that the antiseptic treatment of smallpox by means of external applications is nothing more than the revival of an old practice that was employed and abandoned many years ago.

When the eruption reaches the vesicular stage there is usually experienced considerable burning, particularly of the face, hands and forearms. For the purpose of preventing or alleviating this symptom, some ointment or oily substance will be found useful. Vaseline containing about 3 per cent of carbolic acid makes an efficacious ointment; or, if the odor of carbolic acid be objectionable, oil of eucalyptus or thymol may be substituted. A preparation which we have frequently employed is composed of equal parts of lime water and olive oil, to which is sometimes added an antiseptic and perhaps a little cologne water. This is freely applied with a large camel-hair brush.

When the burning sensation and pain are severe there is perhaps nothing which gives so much relief as cold applications, such as cloths wet with cool water and spread over the face and arms. Curschmann believes that cold and moisture are the most efficient remedies for this condition. He says: "In severe cases the application of iced compresses to the face and hands, or to any part where the eruption is abundant, will diminish the severe pain, lessen the swelling and redness of the skin and make the patient more comfortable."

Moore advises the application over the face of a "light mask of lint thoroughly soaked in a mixture of iced water and glycerin (1 tablespoonful of the latter in 1 ounce of water) and covered with oiled silk."

The development of the eruption in the thick skin of the palms of the hands, tips of the fingers and soles of the feet not infrequently gives rise to great pain. Cold applications or iced compresses may prove of service in this condition, although we think we have seen greater benefit follow the use of luke-warm hand and foot baths. The frequent application of flannel cloths wrung out in tolerably hot water, or the use of hot poultices, is often of great service.

The topical applications recommended for the pustular condition of the skin are numerous. To assuage the pain, burning and itching, to correct the offensive odor, to guard against septicemia and to prevent pitting are the principal ends aimed at in the selection of these measures.

During the period of suppuration the sensation of itching is quite as intolerable as the pain, so that it is almost impossible for the patient to refrain from scratching. In consequence of this, or from other causes, the pustules become ruptured in many localities and their contents discharged. This purulent material undergoes decomposition and gives rise to a highly offensive odor. Remedies are demanded to

relieve the itching and correct the odor. Antiseptic and antipruritic washes, such as carbolic acid (1 to 100), or corrosive sublimate (1 to 1000), may be employed for this double purpose. About the mouth, nose and eyes a saturated solution of boric acid in rose water may be freely used. We have frequently employed a 5 per cent solution of either carbolic acid or Labarraque's solution, directing that both the patient and the bedding should be sprayed with this solution every two hours.

We have sometimes been able to lessen or modify the horrible odor by using as a dusting powder, subnitrate of bismuth, boric acid and, sparingly, iodoform. To either of these, and especially to the latter, talc might be added. We have also derived advantage from a dusting powder composed of 15 to 20 parts of aristol to 100 parts of talc.

MacCombie strongly counsels the early removal of the crusts, which he asserts can best be accomplished by the use of a linseed-meal poultice, sprinkled with iodoform. "On the face the method most agreeable to the patient is to cut a mask of a single thickness of lint, with apertures for the nose, mouth and eyes; then to smear a thin layer of linseed-meal poultice on this, taking care to put on the surface a little vaseline in which iodoform has been mixed, and to apply this poultice to the face, changing it at least every two hours." (Moore.)

Various, indeed, are the methods that have been recommended for the *prevention of pitting in smallpox*, and yet we think it can be truly said that no one of them has stood the test of experience. From the unmodified form of the disease disfigurement is as great and as much dreaded at the present time as it was in the days of our ancestors, and it seems probable that this will continue to be the case until some agent is found capable of causing the eruption to abort before it reaches the pustular stage, for the suppurative process at this stage is attended with destruction of cutaneous tissue and consequently scarring must follow.

The results which, *in our experience*, have followed the use of the so-called ectrotic measures have by no means been encouraging. Perhaps one-half of our patients have recovered from smallpox without permanent scarring, but the result in these cases would have been the same if simply lard or cold cream had been applied to the face, or, indeed, if no application at all had been made. In the severe confluent cases no remedy has been successful in preventing pitting, although we have tested practically all of the more highly recommended measures.

We feel strongly inclined to agree with Gregory, who said: "There is no peculiar method which can be devised for the prevention of pits and scars. The masks and ointments formerly in use for that purpose, and so highly vaunted, are in reality more hurtful than beneficial. The application of a little cold cream to the hardened scales is all that can be recommended."

We have had the skin in the papular stage of the eruption thoroughly washed with soap and water, alcohol and ether, and bichloride of mer-

cury, and then covered with ichthyol-collodion, the last-named application being applied twice a day. This antiseptic treatment did not seem to interfere in any way with the formation of the pustules, for they grew up through the ichthyol varnish.

The remedy which appears to have accomplished most in our hands, is the *tincture of iodine*. We do not make the extravagant claims for this application that some writers have done, but we do think that it has been a little more useful than anything else that we have employed. Our habit has been to paint the face as early as possible with the undiluted tincture of iodine and to continue the application once or twice a day according to the sensitiveness of the skin. Most patients bear the painting very well, although many complain of smarting for a time after the treatment. In some patients the skin is so sensitive that this mode of treatment has to be abandoned, although a tincture of one-half the usual strength might be applied in such cases. About the eighth to the tenth day of the eruption, in unmodified cases, a thin, dry, parchmenty mask is formed which begins to crack and peel off. At this time it will be found advisable to substitute an unguentous application. We believe that the iodine treatment tends to shrink the pustules, to hasten decrustation and, to some extent, to lessen the pitting, although in severe cases it will not prevent it. The liability to consequent pyogenic complications of the skin appears to be diminished. A notable feature of this treatment is that it completely destroys the offensive odor arising from the areas of skin to which the iodine is applied.

We have also obtained good results from mild emollient ointments, with or without antiseptic ingredients. We are not sure that any special combination is essentially more useful than plain petrolatum or cold cream. In the early stages of the eruption these applications are quite grateful to the skin, and later on they serve to soften the purulent débris, which can then be more easily removed from the face. In severe cases, where the treatment of the face is neglected, the odor is more offensive, and the ulcerations appear to be deeper and followed by more disfiguring pitting.

We have frequently incorporated carbolic acid, aristol, biniodide of mercury, etc., in the ointments applied. As above stated, however, these did not seem to materially increase the efficiency of the applications. To soften the crusts from the skin, nothing is better than a salve of the following composition:

℞—Sodii bicarbonatis . . . . . ʒij
Petrolati . . . . . q.s. ad ʒj

We have found great benefit to result from the use of baths given during the stage of pustulation and desiccation. These may be made antiseptic by the addition of creolin (1 to 500) or bichloride of mercury (1 to 10,000 to 1 to 20,000). The purulent accumulations and crusts are detached from the skin by the baths, and the associated septic

fever is greatly lessened. Furthermore, the liability to pyogenic skin complications is diminished. When it is inconvenient or impossible to employ antiseptic baths, much good will often be derived from opening and evacuating the pustules and washing the bases with absorbent cotton saturated with a 1 to 5000 solution of bichloride of mercury.

When extensive impetigo exists we employ a bichloride bath and then dust the patient with a weak aristol or iodoform talcum powder. An ointment which will be found useful in treating impetigo pustules is:

℞—Hydrargyri ammoniati	gr. x
Pulv. amyli,	
Pulv. zinci oxidi	āā ʒij
Petrolati	ʒss

Treatment of Eye Complications.[1]—As a matter of daily routine the eyes should be flushed copiously with warmed, weak, salt or boracic acid solutions. The edges of the eyelids should be anointed with vaseline. In all examinations of the eyes great care must be used in the manipulation, lest the cornea be injured.

In the early stages, when the eyes are hot and flushed and feel heavy, a douche or spray of ice-cold water often brings relief. In excessive hyperemia frequent bathing with water as hot as can be borne will have a soothing effect. In other cases cloths saturated with lead water and laudanum, or ice-cold compresses may be laid upon the closed lids.

The conjunctival sac should be frequently flushed with warm boracic acid solutions. At bed-time the edges of the lids should be anointed with vaseline or with yellow oxide of mercury in vaseline, 1 gr. to the dram, to prevent their becoming glued together.

When conjunctivitis sets in with a mucous or muco-purulent discharge, mild astringents should be used; saturated solutions of boracic acid, to which may be added a few grains of sodium chloride, can be employed. The lids are to be inverted and the mucous surfaces painted with weak solutions of silver nitrate (1 to 5 gr. to the ounce) or protargol or argyrol in 5 to 10 per cent solution may be satisfactorily employed. In some instances the discharge may be so free that stronger astringents must be used. Here no more efficient remedy than silver nitrate can be applied, for in its action it is germicidal as well as caustic. When the lids are tense and board-like, however, and their mucous surfaces covered with a gray film or false membrane, it is not to be used, but only when the lids are relaxed, the discharge creamy, the conjunctiva red and the retro-tarsal folds puckered. After thoroughly cleansing them the conjunctival surfaces should be brushed daily with strong silver solution, 10 to 20 gr. to the ounce; the excess of the drug is to be washed away by an abundance of common salt solution.

[1] The section on the Treatment of Eye Complications was kindly prepared for us by Dr. Burton K. Chance, whom we frequently called in consultation some years ago to advise us in the treatment of severe ocular lesions at the Philadelphia Hospital for Contagious Diseases.

These washings are to be repeated until the membrane is clear and red, and as long as the discharge is abundant the use of silver is indicated.

The edges of the lids are to be greased with vaseline, and they are then to be restored to their normal position. The pressure on the globe caused by the swollen lids may be so great as to necessitate the cutting of the outer canthus. A canthotomy may have to be done also, to facilitate the examination of the conjunctiva and the cornea.

Persistent and increasing chemosis of the conjunctiva demands snipping in order to relieve the pressure on the cornea.

When the lids are tense and the secretion flocculent, the local application of cold is most useful.

When the *cornea* is involved great care must be exercised during any manipulation, lest pressure be exerted on the globe.

Efforts at cleanliness must be redoubled. Solutions of atropine of 4 gr. to the ounce are to be used twice or thrice daily, to effect complete mydriasis, when the ulceration is central. But if the ulceration be marginal eserine salicylate in weak solution, $\frac{1}{4}$ gr. to the ounce, may be used, but with great carefulness, as this drug is liable to increase the hyperemia of the iris, with consequent iritis. Therefore, the use of this drug should be discontinued when the pupil has become contracted. Ice must be discontinued and hot compresses are to be substituted. Squares of gauze wrung out of water which is kept at about 110° F. are to be frequently applied.

Where *perforation of the cornea* is threatening, the edges of the ulcer must be cauterized at once. Here a dull hot probe, thoroughly applied, may end the process. We have used, besides the hot probe, solutions of carbolic acid, of iodine and crystals of trichloracetic acid. If there be not too much conjunctival secretion, a well-applied roller bandage may afford the proper support to the already weakened corneal membrane.

A low grade of conjunctivitis may persist for a week or even months after convalescence from smallpox in persons whose illness has been complicated by serious conjunctival inflammation. Here the use of stimulating astringents like the boroglyceride or the glycerole of tannin act with signal advantage. Argentamin, 2 to 5 per cent, largin, or argyrol, 5 to 10 per cent, may be tried.

Formalin, 1 to 5000, or bichloride of mercury, $\frac{3}{4}$ gr. to the pint, may be used with success in more severe cases with considerable discharge.

CHAPTER VI.

CHICKENPOX.

Synonyms.—*Varicella;* formerly, *Variola crystallina, Variola notha, Variola spuria.* English, formerly, *water pock, glass pock;* German, *Varicellen, Wasserpocken, Wind blättern, Schafpocken;* French, *la varicelle, la verolette;* Italian, *Merviglione, ravaglione.*

Definition.—Chickenpox is an acute, highly contagious disease, occurring chiefly in children, characterized by an eruption of vesicular type, appearing in crops and accompanied by mild febrile disturbance, which usually begins with the appearance of the cutaneous outbreak. The lesions dry in a few days into crusts. One attack protects for life in the vast majority of cases.

History.—Chickenpox is doubtless a disease of great antiquity, although for centuries it was confounded with smallpox. The Arabian physician, Rhazes, who lived in the ninth century, made mention of a mild or spurious eruption which was not protective against epidemic smallpox. The Sicilian physician, Ingrassias, seems to have been the first to have described varicella in accurate terms; this appeared in a work entitled *Preternatural Swellings*, written in 1553. Vidus Vidius, an anatomist and physician, wrote some forty years later, employing for varicella the term *crystalli* or *variolæ crystallinæ*, a designation which clung to the disease for many years.

Sydenham makes no mention of the disease. An admirable description, which admits of no room for doubt, has come down to us from the pen of Riverius, who wrote in 1646.

Morton used the term *chickenpox*. This appears to be the first mention of this term in literature. The name *chickenpox* is said to be derived from the word *cicer*, a chicken-pea, the French word for the same being *chiche*.

THE ETIOLOGY OF CHICKENPOX.

While the etiological agent of varicella has never been isolated or identified, yet evidence has accumulated to indicate that it is probably a living active transmissible and filterable agent or virus occurring in the blood or vesicular fluid of the disease. Salmon,[1] Tyzzer[2] and Teissier, Gastinel and Reilly[3] were unable to obtain a specific reaction

[1] Compt. rend. Soc. de biol., 1905, **48**, 262.
[2] Jour. Med. Res., 1905–1906, **14**, 361.
[3] Compt. rend. Soc. de biol., 1922, **76**, 73.

on rabbits' corneas inoculated with fresh fluid from varicella vesicles, and Swellengrebel,[1] Bertarelli[2] and Gins[3] have observed more or less specific cellular changes following inoculation with vesicle lymph. Park,[4] Martin[5] and Tyzzer[6] were unable to transmit varicella to monkeys, but Rivers and Tillett[7] have recently reported the successful inoculation of rabbit testicles by the injection of 2 cc. of blood from patients with chickenpox usually taken during the first twenty-four hours after the appearance of the eruption. By transferring the virus from rabbit to rabbit, at intervals of four days, its virulence was increased and found capable of producing lesions in the cornea and skin. It was found by Rivers and Tillet[8] to be filterable through Berkefeld N and V filters and inactivated by heating for ten minutes at 55° C. and three different strains have proven immunologically distinct from cowpox virus and the virus of symptomatic herpes, but unfortunately there is no evidence to indicate that it bears an etiological relationship to varicella. However, this hitherto unknown transmissible agent has been found by Rivers and Tillett[9] to partake of the characters of the so-called filterable viruses and nuclear inclusions have been observed in the testicles of vervets inoculated with emulsified tissue of human varicella lesions. Tezner[10] has also demonstrated a transmissible agent in varicella lymph by intraspinal injection of rabbits. Auricchio[11] and Nasso and Laurinsich[12] regard the Di Cristina bodies as the cause of chickenpox, but this work requires further investigation and confirmation.

Age.—Chickenpox is essentially a disease of early childhood. It is most common between the ages of one and seven years. Although it develops at times in infants at the breast, they more commonly escape the infection when exposed to it. The statement made by many authors that chickenpox is excessively rare in adults requires qualification; this view has been so commonly held for many years that we have deemed it advisable to discuss the subject of adult varicella under special caption. Welch and Schamberg saw two score or more cases of chickenpox in adults, and similar experiences have been reported by others. The most advanced age at which we have seen the disease is forty-nine years. The youngest period at which varicella appears to have been observed is recorded by Senator, who saw an infant of eleven days with the disease.

[1] Arch. Hyg., 1911, **64**, 164.
[2] Centralbl. f. Bakteriol., orig., 1909, **1**, 181.
[3] Ztschr. f. Hyg. u. Infectionsk., 1918, **76**, 299.
[4] Trans. Assn. Am. Phys., 1902, **17**, 217.
[5] Compt. rend. Soc. de biol., 1905, **48**, 263.
[6] Loc. cit.
[7] Jour. Exper. Med., 1923, **38**, 673.
[8] Ibid., 1924, **39**, 777.
[9] Ibid., 1924, **40**, 281; 1926, **43**, 275.
[10] Monatsch. f. Kinderlik., 1924, **28**, 39.
[11] Pediatria, 1924, **32**, 1305.
[12] Ztschr. f. Kinderhk., 1925, **39**, 516.

The following table, compiled by Gee[1] from the records of the Children's Hospital of London, shows the age incidence among children:

	Boys.	Girls.	Total.
Under 1 month	2	0	2
2 months	2	6	8
3 "	4	9	13
6 "	29	28	57
12 "	45	52	97
18 "	34	28	62
2 years	36	39	75
3 "	36	42	78
4 "	47	53	100
5 "	44	52	96
6 "	33	25	58
7 "	19	11	30
8 "	10	19	29
9 "	4	6	10
10 "	3	2	5
12 "	1	6	7
	349	378	827

Varicella prevails more at certain times than at others and may occur in epidemics. In large centers of population, however, the disease is like scarlet fever, endemic, and to a certain extent always present. The mildness of chickenpox favors its dissemination, inasmuch as children frequently attend schools while still in an infectious state.

Susceptibility is not influenced by race, the negro and the Caucasian taking the disease with equal facility. Neither does varicella seem to be influenced by climate or season.

While varicella is extremely contagious, its infecting power is not as intense as that of measles or smallpox, and it is an easier disease to control by isolation. As far as we know, the infection gains entrance to the individual through the respiratory tract. In the vast majority of cases chickenpox is contracted by direct exposure to a person suffering from the disease. It is not impossible that the affection may be carried by a third person or through the agency of infected objects, but this is in all probability uncommon. It is possible for the disease to be transferred before the appearance of the eruption; this is exemplified in the following case:

A physician's daughter, aged sixteen years, developed a slight sore throat and a little fever, and was isolated in a room in the upper story of her home. A small whitish patch was noticed on the posterior pharyngeal wall. On the following day the eruption of chickenpox appeared. An eight-year-old brother who was with the patient on the previous day was kept in a distant part of the house, out of all communication with the sister or her attendants. Sixteen days after exposure, the same having taken place before the appearance of the eruption, the boy developed chickenpox.

It is not surprising that varicella should occasionally be communi-

[1] Reynold's System of Medicine, American edition, Philadelphia, 1879.

cated before the appearance of the cutaneous outbreak, when we remember that smallpox may be transmitted during the initial stage of the disease.

How long a patient remains capable of transmitting the infection has not been definitely determined. Nor is it known whether the infective agent is present in the crusts, as is the case in smallpox. In the absence of positive knowledge on this point, it is wise, in order to prevent contagion, to isolate the patient until the skin is entirely free of the original crusts. Crusts due to secondary infection of the skin are not capable of transmitting the disease.

Second attacks of chickenpox are of great rarity. Thomas never observed a second attack, an experience which corresponds with ours. Gerhardt is said to have treated a child with three attacks, and a similar observation is recorded by Heim. Vetter states that he saw the child of a physician who had two attacks of chickenpox within fourteen days. Neale[1] reports a second attack of varicella after an interval of ten days. Trousseau, Boeck, Kassowitz, Hufeland and Canstatt have also reported cases. Berinsohn[2] states that among 250 cases of varicella observed over a period of fifteen years there was only one second attack. These isolated instances do not, however, controvert the general experience of physicians that one attack of chickenpox, in the vast majority of instances, protects against future attacks.

Inoculability of Varicellous Fluid.—Steiner[3] obtained results very different from those above referred to. He claims to have inoculated 10 children, 8 of whom developed typical chickenpox. The time elapsing between the inoculation and the appearance of the eruption in these cases was eight days.

If the possibility of transmission of the disease in the usual manner was entirely excluded in Steiner's cases, his observations go very far toward proving that chickenpox can be communicated by inoculation. In view, however, of the negative results obtained by nearly all other investigators, future experiment will be necessary to confirm the successful inoculations obtained by Steiner. Hess and Unger[4] have failed to produce the disease in normal children by inoculating them upon the mucous membranes of the nose and throat with vesicle lymph and material collected from the nose and throat of patients with chickenpox or by inoculating them intracutaneously, subcutaneously or intravenously with fresh vesicle lymph.

Period of Incubation.—The stage of incubation of chickenpox is ordinarily longer and more variable than that of smallpox or measles. Different observers assign rather variant limits to this period, as will be seen by reference to the following quotations:

[1] Lancet, 1891, vol. ii.
[2] Herpes Zoster and Varicella, Nederl. Tijdschr. v. Geneesk., 1924, No. 19, p. 2097.
[3] Wien. med. Wchnschr., 1875, No. 16.
[4] Am. Jour. Dis. Child., 1918, **16**, 34.

Gregory[1] says "it does not exceed four days and is certainly less than a week;" Heberden[2] places it at eight or nine days; Trousseau,[3] fifteen to twenty-seven days;" Gee,[4] "at about a fortnight;" Thomas,[5] "thirteen to seventeen days;" Delpech, twelve days; Holt,[6] "quite uniformly from fourteen to sixteen days;" Corlett,[7] ten to nineteen days.

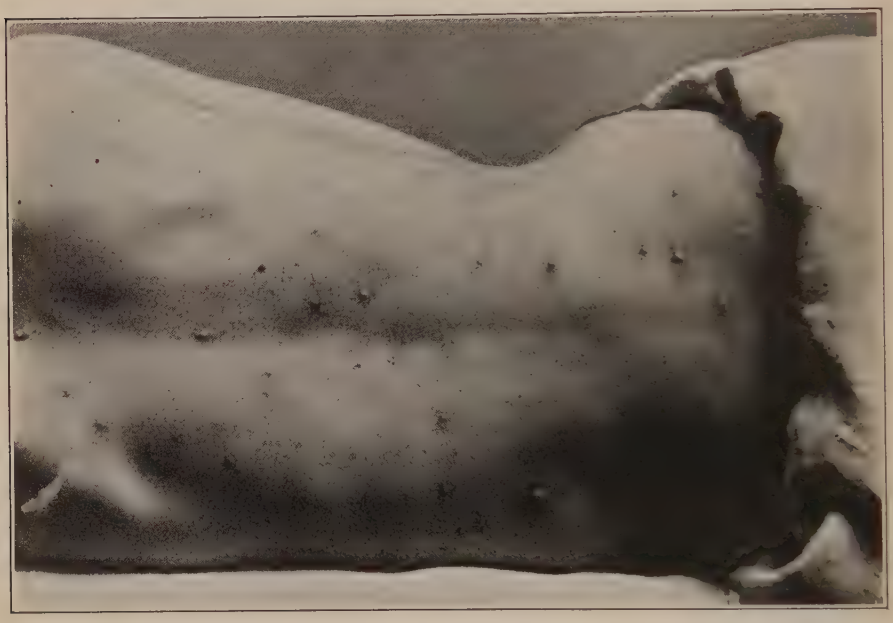


Fig. 77.—Chickenpox vesicles surrounded by reddish areolæ.

Our experience would lead us to regard fourteen to seventeen days as the usual period, although we have observed it to extend over nineteen days and even as long as twenty-one days. It is possible that in rare cases it may be less than ten days and longer than three weeks.

In 16 cases occurring in an outbreak in the Municipal Hospital we were able to fix the incubation stage quite accurately. The periods were as follows:

	Cases.		Cases.
13 days	1	18 days	1
14 "	7	19 "	1
15 "	3	21 "	1
17 "	2		

[1] Lectures on the Eruptive Fevers, first American edition, 1851, p. 295.
[2] Quoted by Gee: Loc. cit.
[3] Lectures on Clinical Medicine, American edition, Philadelphia, 1882, p. 136.
[4] Reynold's System of Medicine, American edition, Philadelphia, 1879, p. 125.
[5] Ziemssen's Encyclopedia of Medicine.
[6] Diseases of Infancy and Childhood, p. 929.
[7] Acute Infectious Exanthemata, p. 165.

Steiner, who claims to have successfully inoculated varicella in 8 patients found the incubation stage in these patients to be uniformly eight days. During the incubation period there are, as a rule, no evidences of disturbed health. Now and then, however, as in some of the other exanthemata, the breeding of the disease may give rise to slight symptoms, such as loss of appetite, lassitude and general indisposition.

IMMUNITY.

Chickenpox, or varicella, occurs only in man; the lower animals enjoy an absolute natural immunity even when intimately exposed to infection.

The disease is most common between one and seven years, but may develop in nursing infants. Adults commonly escape, but those who have not had the disease in childhood are susceptible and may develop the disease.

Both sexes and all races are equally susceptible. Human beings do not appear to have an appreciable degree of natural immunity, although the disease does not attack as many persons as are infected with measles.

One attack usually confers a lasting immunity; second attacks have been recorded, but are exceedingly rare.

Complement-fixation in Chickenpox.—In 1916 Kolmer[1] showed for the first time that complement-fixing antibodies occurred in the blood of chickenpox patients when tested with saline antigens of crusts or vesicle contents; 30 to 39 per cent of patients from the fourth to forty-second day of the disease yielded positive reactions. These were found to be specific in that positive results were not observed with cowpox and smallpox sera with the varicella antigens.

However the percentage of positive reactions and degree of complement-fixation were regarded too small to be of diagnostic value, although Girard[2] subsequently stated that the tests were of value for purposes of differential diagnosis. De Lange[3] has reported positive reactions with varicella antigens and the sera of cases with herpes zoster, and on this basis concludes that the etiological agents of the two diseases are identical; Netter[4] has reported similar results and states that the relationship between varicella and herpes zoster is as certain as between vaccinia and smallpox. But Landa and Silberstern[5] observed negative complement-fixation reactions in herpes zoster with chickenpox antigens and suggest that the positive results obtained by the French workers might have been due to an epidemic of zoster of chickenpox origin in Paris.

[1] Jour. Immunol., 1916, **1**, 51.
[2] La Reaction de Deviation Dans la Varicelle, Paris, Jouve & Co., 1918.
[3] Klin. Wchnschr., 1923, **2**, 879.
[4] Paris méd., June 7, 1924, p. 521.
[5] Klin. Wchnschr., 1925, **4**, 1871

Vaccination Against Chickenpox.—The virus of chickenpox occurs in the vesicle fluid in a very dilute state and appears to quickly lose its virulence; therefore, the results of vaccination in this disease have varied a great deal in the hands of different investigators. Steiner[1] reported negative results in 1875, but Kling[2] has reported the successful inoculation of chickenpox followed by protection. The virus should be the clear fluid of vesicles in as early stage as possible both of the disease as well as of the vesicles themselves, and taken, of course, only from children otherwise healthy and free of syphilis and tuberculosis. Kling cleanses a vesicle, inserts the point of a sterile lancet and makes three to four pricks of the cleansed skin of the arm of the child being vaccinated; three or four more insertions are made of virus from a second vesicle. The mild traumatic reaction subsides in a day or two, followed on the eighth day, as a rule, by the development of one or more red papules which quickly change to vesicles, followed by scabbing and eventually an insignificant scar. In a small percentage of cases a generalized eruption and slight fever may occur. Of 135 vaccinations failures occurred in 23 per cent. These experiments indicate that it is sometimes possible to inoculate and transmit chickenpox by this means and that the resulting infection is usually local.

According to Kling, successful inoculation confers immunity, while 73 per cent of unvaccinated children contract the disease. Handrick,[3] however, was unable to confirm these results during two epidemics with the vaccination of 127 children. In this country Rabinoff[4] inoculated 142 susceptible children using Kling's method except that scarifications were employed; 114, or about 75 per cent, developed varicella. Of these, 6, or 8 per cent, subsequently developed the disease, all being vaccinated within ten days previously and within the incubation period. Rabinoff is convinced that the vaccinations limited the spread of the disease. Michael[5] has reported 8 successful inoculations of 32 children by this method.

Hess and Unger[6] have vaccinated by drawing the fluid of vesicles (not pustules) into sterile capillary tubes to the distance of about 1 inch, diluting the sterile saline solution and injecting intravenously. In all, 38 children, aged three or four years, were inoculated by this method; none developed any local or general symptoms or any eruption suggestive of varicella. All were exposed to chickenpox; 1 developed the disease thirty-six days after vaccination.

Lapidus,[7] Meyer,[8] Gyr[9] and Hotzen[10] have also reported positive results in some cases and Greenthal[11] has recently stated that of 36

[1] Wien. klin. Wchnschr., 1875, **25**, 306.
[2] Berl. klin. Wchnschr., 1913, **1**, 2083; 1915, **42**, 13.
[3] Monatsch. f. Kinderheilk., 1914, **13**, 205.
[4] Arch. Pediat., 1915, **32**, 651.
[5] Boston Med. and Surg. Jour., 1917, p. 702.
[6] Am. Jour. Dis. Child., 1918, **16**, 34.
[7] Monatschr. f. Kinderh., 1916–1917, **14**, 237.
[8] Ibid., 1918–1919, **15**, 184.
[9] Ibid., 1916–1917, **14**, 310.
[10] Ibid., 1918–1919, **15**, 576.
[11] Am. Jour. Dis. Child., 1926, **31**, 851.

individuals vaccinated with vesicle lymph, 19 showed "takes," while 16 reacted negatively but that no cases of varicella developed in any. The use of varicella crusts as vaccine was not successful in the few instances in which it was tried.

These results indicate that cutaneous inoculation is possible with the production of active immunization in some cases at least, but the disease is usually so mild that vaccination is not required as a practical measure despite the fact that it is a cause for loss of time from schools and may be troublesome in institutions for children.

Serum Prophylaxis of Chickenpox.—Since passive immunization against measles by injections of convalescent serum has proven so successful in measles, Blackfan, Peterson and Conroy[1] have tried a similar procedure in chickenpox and reported that among 42 susceptible children to whom 5 cc. of convalescents' serum had been given within five days of exposure, 7 contracted a mild form of the disease and 35 escaped without symptoms. They believe the method to be an efficient means of preventing severe epidemics in institutions and recommend it for the protection of children convalescing from acute diseases and those suffering from nutritional disturbances, tuberculosis and chronic diseases.

Weech[2] gave intramuscular injections of 3 to 4.5 cc. of serum from children in whom the disease had developed ten to twenty days previously to 9 infants exposed to chickenpox one to six days previously and all but 1 escaped the disease. Schmidt,[3] however, has reported negative results, but the procedure would appear to be worth trial under exceptional circumstances providing the serum of recent convalescents is available, although the protection does not last over four to eight weeks. The technique is the same as that described later in the chapter on Measles.

In this connection mention may be also made that Sicard and Paraf[4] have reported that injections of serum from herpes zoster convalescents do not protect against chickenpox, although Lipschütz and Kundratitz[5] state that it does.

THE SYMPTOMATOLOGY OF CHICKENPOX.

Preëruptive Stage.—In the vast majority of cases chickenpox is not preceded by a prodromal illness. The onset of the constitutional manifestations is usually coincident with the appearance of the eruption. The ordinary history elicited from mothers is that the eruption is the first symptom to attract their attention, and that the children are not ill prior to this time.

[1] Ohio State Med. Jour., 1923, **19**, 97.
[2] Jour. Am. Med. Assn., 1924, **82**, 1245.
[3] Med. Klinik, 1924, **20**, 642.
[4] Bull. et mém. de la Soc. méd. d. hôp., 1925, **49**, 301.
[5] Wien. klin. Wchnschr., 1925, **38**, 499.

At the Philadelphia Hospital for Contagious Diseases we have had the opportunity of studying the temperature records of a number of chickenpox patients before the appearance of the eruption; these patients were convalescent from scarlet fever when they developed varicella. In almost every instance the temperature remained about normal until the chickenpox eruption appeared and, indeed, in some cases even after the lesions had developed.

In a small percentage of cases some little constitutional disturbance may be observed a day or two before the appearance of the exanthem. This consists of slight rise of temperature, anorexia, vague pains and chilliness. More common is it to discover these symptoms a half-day or so before the eruptive outbreak. During the night preceding the appearance of the exanthem the child may be slightly feverish and restless. But these mild precursory symptoms should not be regarded as representing a prodromal illness, for by this term as applied to smallpox is meant a distinct stage preceding by two or three days the onset of the eruptive phenomena.

It is important, however, to call attention to the fact that varicella in adults may occasionally be preceded by a prodromal stage. While most of these patients give no history of a preëruptive illness, a minority of them will volunteer such information. We have seen perhaps a half dozen of adults suffering from varicella who had distinct prodromata. These symptoms consist usually of chilliness, lassitude, anorexia, nausea, slight headache and backache and some elevation of temperature (101° to 102° F.). These manifestations may precede the appearance of the eruption by two or three days, though more often not longer than twenty-four hours. It is rare to observe high fever, vomiting, severe lumbar pain and prostration — symptoms which usher in a well-pronounced smallpox.

In general, it may be said that a true prodromal stage in children suffering from chickenpox is extremely rare; in adults it is by no means so infrequent. When it does occur it is much milder than the prodromal illness ordinarily observed in smallpox. A *prodromal erythema* is, in rare cases, seen before the appearance of the varicellous eruption, as it is at times before the eruption of smallpox and measles.

Thomas observed "just before the outbreak of a light case of varicella with ephemeral though intense fever (105.8° F., rectal temperature) the appearance of a universal erythema of short duration." He adds, however, that although he watched carefully for these eruptions this was the only one he ever saw.

Henoch is also said to have seen and described such an erythema.

A prodromal scarlatinoid rash preceding the appearance of the varicella eruption was observed by us in a patient admitted into the scarlet-fever ward of the Municipal Hospital in the early part of 1902. A girl, aged five years, was sent to the hospital from a large foster home. She had had vomiting, some elevation of temperature and on admission there was a diffuse scarlatiniform rash covering the entire

trunk. This resembled scarlet fever so strongly that an experienced interne regarded it as the scarlatina exanthem. The rash faded in the course of twenty-four hours and was followed by the appearance of a number of varicella vesicles. At the end of five days after admission to the ward a rise of temperature to 103° F. occurred, accompanied by sore throat and a well-pronounced and typical scarlet-fever rash. It was evident that the child contracted scarlet fever in the ward. No scarlet fever existed in the foster home from which the child was received.

The Eruptive Stage.—As has been stated, the eruption is commonly the first symptom to attract attention to the disease. Synchronously with the appearance of the cutaneous outbreak, or a few hours before or afterward, a varying degree of fever sets in. In some cases this does not reach higher than 99° F.; in others, however, the pyrexial elevation may be most marked. Thomas records one case in which the initial temperature was 105.8° F., and we have on several occasions observed temperatures of 104° and 105° F. This high fever is, as a rule, of brief duration, subsiding in twelve or twenty-four hours to 99° or 100° F. High fever does not necessarily pressage the development of a profuse eruption. We have seen a temperature of 104° F. in a case with scant and abortive lesions.

The temperature commonly falls to normal in the course of one to three days. Where the eruption is copious, however, moderate fever may persist for four or five days. In cases in which the varicellous lesions become secondarily infected; the temperature may continue above normal for a fortnight or even longer.

The Eruption.—The eruption of chickenpox usually appears first on the back or the face, although other regions may be the seat of the initial lesions. Irregular extension then occurs, new lesions developing on different portions of the cutaneous surface. The hairy scalp is nearly always beset with some vesicles.

The *distribution* of the eruption is subject to some variation, but is tolerably uniform in the majority of cases. The trunk, particularly the back, is relatively more profusely attacked than the distal portions of the extremities—the wrists, ankles, hands and feet. The face usually presents a moderate number of discrete vesicles. It is rare for the face to escape completely, although at times but two or three lesions may be present. At other times, in copious eruptions, quite an abundance of lesions may be seen on the face. The arms and legs are seldom profusely attacked except in unusually extensive cases.

It has been claimed by some writers that varicellous lesions do not occur upon the palms and soles. It is true that in most cases the palmar and plantar surfaces are free of eruption; but it is by no means rare to find a few vesicles in these regions, and in severe cases the lesions may be fairly numerous.

The palms and soles are much less frequently and less abundantly involved than in smallpox, in which disease some lesions are nearly

always present in these regions. The dorsal surfaces of the hands and feet are likewise relatively lightly affected compared with the general extent of the eruption. In fact it may be stated that the distal portions

FIG. 78.—Chickenpox lesions in the crusted stage, about the fourth day of the disease.

FIG. 79.—Well-marked chickenpox eruption, showing crusted lesions and recent and old vesicles. Fourth day.

of the extremities usually suffer but little in chickenpox; the eruption prefers the covered surfaces.

The distribution of the eruption may, to some extent, be influenced by irritation of the skin prior to the appearance of the lesions. We

have seen a profuse crop of lesions develop over a rectangular area on the sternum to which a mustard plaster had been applied during the preëruptive period. Any irritant by increasing the vascularity of the skin may attract lesions to the region thus irritated. It is not so common, however, to observe an increase of the eruption from this cause as it is in smallpox. In the latter disease the influence of cutaneous

FIG. 80.—A severe attack of chickenpox, showing lesions in various stages of development (fourth day). Relative sparsity of lesions on the face as compared with the trunk.

congestion in determining an increase of the eruption in a given area is emphasized by frequent experience.

Ordinarily by the time that the physician is called to see a child with chickenpox vesicles are observable upon the body. If the skin is carefully examined early it will be noted that the vesicles are usually preceded by erythematous spots. These are pea- to bean-sized, rosy-

red in color and in appearance not unlike the rose spots of typhoid fever or flea bites. Very soon the centers of the macules become raised and small vesicles are formed which rapidly increase in size. In some cases the rosy macules are elevated, somewhat acuminated and in reality represent papules.

The duration of the transitional lesions before vesiculation takes place is extremely variable. At times some of the lesions of varicella abort in the macular or papular stage and never go on to the development of vesicles. Indeed, Thomas mentions a case, the nature of which was verified by the previous occurrence of varicella in a sister, in which

FIG. 81.—Very mild attack of smallpox resembling chickenpox.

erythematous spots (roseolæ) persisted for thirty-six hours and then disappeared without the formation of any vesicles whatever. Varicella without the development of vesicles must, however, be extremely rare.

Varicellous vesicles may spring up so rapidly that they appear to arise directly from the normal skin. We were enabled to determine in one instance that vesicles developed in less than four hours. A trained nurse bathed a child at 11 A.M. and carefully examined the skin for an eruption without discovering any. At 3 P.M., four hours later, we examined the child and found several fully formed, tense, varicellous vesicles on the trunk.

The lesions often look as if they had been produced by drops of

scalding water sprinkled upon the skin. They are superficially situated, differing in this respect from the deeper-seated vesicles of smallpox. The epidermal roof of the vesicle is thin and readily ruptured.

The vesicles of chickenpox vary greatly in size; they may be no larger than a pin-head or they may reach the dimensions of a large pea. They are commonly tense, although rarely as hard as the variolous vesicle. Slight traumatism, such as is produced by scratching or the friction of clothing, suffices to rupture the vesicle. The fluid from an early vesicle is clear and watery in appearance; later it becomes turbid or lactescent. The vesicles are round or oval, the shape being somewhat determined by the lines of cleavage of the skin. In the axillary and lateral costal regions they are commonly oval, the long axis corresponding with the direction of the ribs.

Chickenpox vesicles are commonly surrounded by a reddish areola. This may be narrow, measuring but $\frac{1}{8}$ inch; in other cases, however, it may have a breadth of $\frac{1}{2}$ inch or more.

Much diagnostic value has been attributed by some observers to the comparative degree of evacuation of chickenpox and smallpox vesicles effected by puncturing them with a needle. While it is true that the varicella vesicle is often completely emptied, and the variolous vesicle, owing to its more multilocular structure, less completely evacuated, but little value should be placed upon this test. There is too much latitude possible in the interpretation of the degree of evacuation effected.

The eruption of chickenpox appears in *crops*. The first outbreak commonly consists of a dozen to fifteen lesions. After an interval of some hours, usually a day or so, a second crop appears which often numerically exceeds the first. Twenty-four hours later a third outbreak may occur and new lesions may thus continue to appear for four or five days or even a week. Owing to the fact that the lesions are of different age, they are seen in varying stages of evolution and involution. There may be present at the same time small, new, tense vesicles, older, drying vesico-pustules and, in addition, dark-colored crusts which represent the remains of the first vesicles. This multiformity is one of the most distinguishing features of the eruption of chickenpox.

The *duration* of the individual lesion of chickenpox is brief. The vesicles, after reaching the acme of their development, become flaccid, and in from one to three days dry into crusts. The unruptured vesicle desiccates first as its central summit. Lesions which are ruptured by mechanical force give exit to a fluid which forms an irregularly-shaped crust.

The fluid contained in the vesicle is at first as clear as water; it later becomes turbid and, finally, if unruptured, quite purulent. During these changes the vesicle which has in the beginning a "dewdrop-like" appearance acquires a grayish or yellowish color.

True umbilication, such as is seen in the early smallpox vesicle, does not occur in chickenpox. There is sometimes seen a pin-point-sized

invagination of the surface of a vesicle due to the presence of a hair follicle. Commonly there is observed a central sinking in of some of the vesicles or vesico-pustules due to partial evacuation and central drying. This is also seen in the late pustular stage of smallpox, and might be called a secondary umbilication.

As the vesicles of chickenpox begin to dry there not infrequently develops a flat, vesicular, spreading ring upon the border of the crust; beneath the raised-up epidermis is a little puriform fluid. The lesions may, as a result of this process, spread to the size of a silver quarter or half dollar. This condition is extremely common in smallpox and has been called "impetigo variolosa." The process being the same in chickenpox, the condition might be appropriately designated "impetigo varicellosa." The cause of these spreading sores is an infection of the varicellous sites with streptococci and staphylococci present upon the surface of the skin. In extensive eruptions where there is much of this impetigo moderate elevation of temperature may develop, giving rise to a secondary fever.

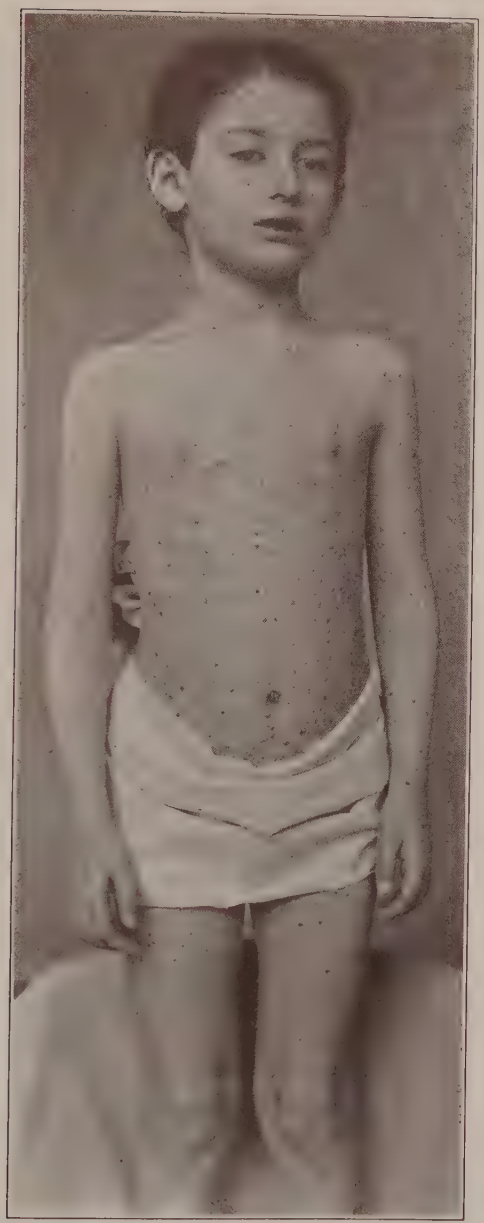
The *extent* of the varicellous eruption is extremely variable. The total number of lesions in some cases may amount to but a half dozen; on the other hand, they may cover almost completely the entire cutaneous surface and number hundreds or even thousands. Thomas says, "as many as 800 have been counted or estimated. In a copious eruption in a young boy we counted 1400 lesions; shortly afterward in an older lad convalescent from scarlatina we encountered a much more extensive eruption. A photograph of this boy is shown in Plates XII and XIII. We estimated that there were in the neighborhood of 3000 lesions upon the skin.

While neighboring and closely set vesicles may occasionally coalesce, one never sees a confluence of the lesions such as is observed in smallpox.

Scarring After Varicella.—It is not uncommon for some varicella lesions to be followed by scars. Indeed, it is rather the rule for patients to have one or several cicatrices which persist after the disappearance of the eruption. These are from pin-head- to pea-sized, rounded or oval, and excavated to a variable degree. In severe cases the number may reach a half dozen or a dozen or more. They are never, however, as numerous as is seen in smallpox. The scars result from a destruction of the papillary layer of the true skin; this may be due to secondary infection as a result of scratching, but it may occur entirely apart from this cause. Chickenpox vesicles at times break down early and produce a necrosis of the underlying corium; the ulcer left heals with the formation of a depressed scar. Occasionally a hypertrophic scar or sort of keloid forms at the site of these losses of tissues.

The *mucous membranes* are not infrequently the seat of varicellous lesions. It is quite common to find a few vesicles upon the soft and hard palate, and these in doubtful cases are of diagnostic importance.

PLATE XII



An Unusually Extensive Eruption of Chickenpox in which the Lesions were Estimated to Reach 3000 in Number.

PLATE XIII

Extensive Eruption of Chickenpox. Same patient as Plate XII.

Lesions are also occasionally noted upon the buccal mucous membrane, tongue and posterior pharyngeal wall. Situated in these regions, the flaccid roof of the vesicle soon ruptures, leaving at first a grayish pellicle of epithelial débris and later a circumscribed superficial abrasion, surrounded by a reddish areola and resembling to some extent the sore of aphthous stomatitis. The eruption in the mouth is usually scant, even in cases characterized by an abundant cutaneous outbreak. The exanthem, as a rule, appears synchronously with the eruption on the skin, but it may precede it. We know of a colleague who was perplexed by the appearance of a circumscribed patch on the posterior pharyngeal wall of his daughter, but who later discovered that it was an early varicellous lesion preceding the general eruption by about twelve hours.

Henoch has seen varicellous vesicles on the gums and also on the conjunctival mucous membrane. Thomas observed the latter attacked only when the contiguous portion of the eyelid was affected. He likewise under similar conditions noted involvement of the nasal mucous membrane.

Marfan and Halle have recorded 2 cases of involvement of the larynx, one necessitating tracheotomy. The other case succumbed to other complications and on autopsy the remains of a vesicle were found on the right vocal cord.

Varicellous lesions are occasionally found in the vestibule of the vagina and upon the prepuce, in which regions the accompanying swelling may cause difficulty in micturition.

As far as is known, chickenpox never attacks the mucous membrane of the stomach or intestines. Partridge, in 1887, presented to the New York Pathological Society specimens from a child that had died of varicella complicated by bronchopneumonia. In the large intestines were a number of excoriations which were regarded as chickenpox lesions.[1] This child had diarrhea during life, and to our minds it is highly improbable that the intestinal lesions were of a varicellous nature.

Varicella in Adults.—We have preferred to consider chickenpox in the adult under special heading in order to give greater prominence to the opinion that the frequency of this disease in adults has been underestimated. The assertions of many writers of prominence have caused varicella in adult life to be regarded as a *rara avis*. Thomas, whose teachings are based upon a large and well-digested experience, states: "Varicella is a disease of childhood, and attacks by preference young children and even sucklings. In children over ten years of age attacks are infrequent, and *I never saw an adult suffering from varicella*." And again, "The predisposition (to varicella) is wont to vanish of itself spontaneously about the eleventh year."[2] Von Jürgensen[3] remarks:

[1] Quoted by Jennings: Keating's Cyclopedia of Diseases of Children, p. 761.
[2] Thomas: Ziemssen's Cyclopedia of Medicine, American edition, 1875, pp. 8 and 27.
[3] Nothnagel's System of Medicine, American edition, p. 288.

"With regard to the differences between variola and varicella, it is important to state that the latter is, if not wholly, yet practically limited to the age of childhood—the first ten years of life;" and further on, "Varicella is a disease which is quite peculiar to the age of childhood."

FIG. 82. Chickenpox in an adult; second day.

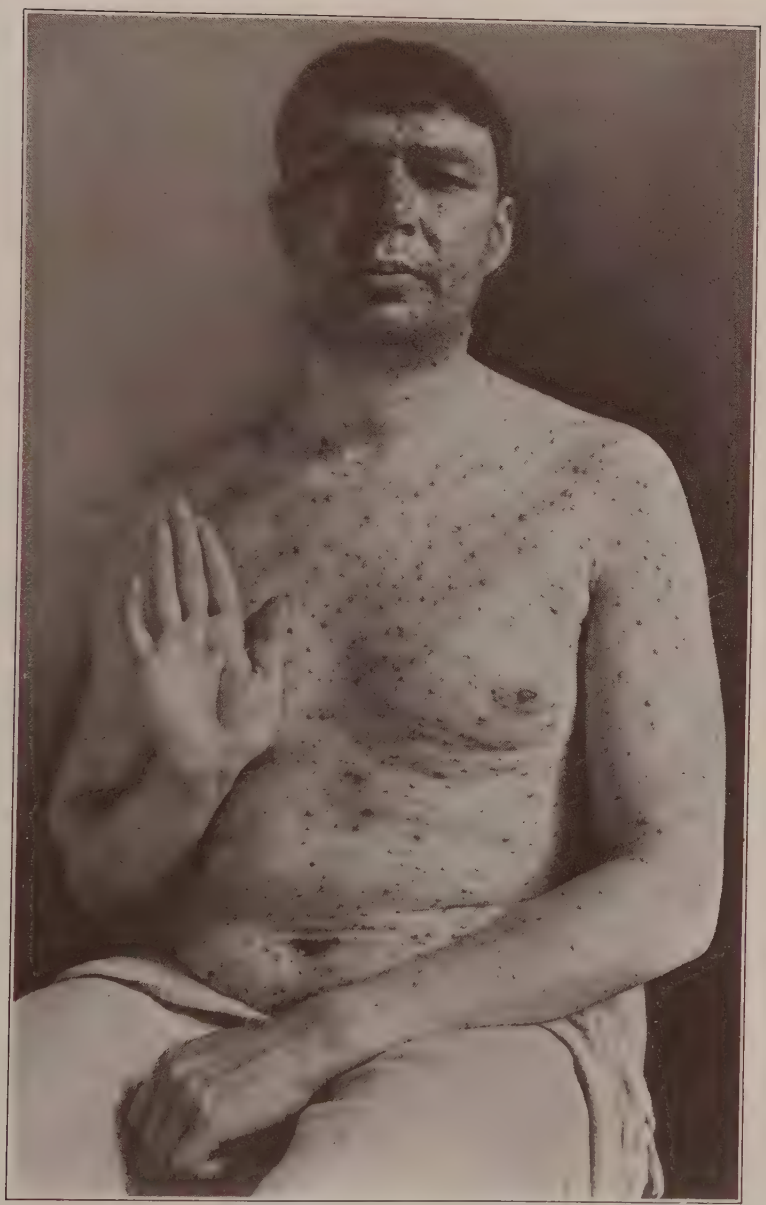
FIG. 83.—Chickenpox showing multiformity of lesions.

Jonathan Hutchinson,[1] in a wide experience, saw 1 or 2 cases about the age of twenty, and states that "A point of great interest in varicella is the almost complete immunity of adults."

Bohn encountered chickenpox but once in an adult, in a patient aged sixteen years, and J. Lewis Smith likewise saw but 1 case. Corlett[2]

[1] Quoted by Smith, J. L.: Medical and Surgical Diseases of Childhood, 1896, p. 229.
[2] Infectious Exanthemata, Philadelphia, 1901, p. 165.

PLATE XIV



Chickenpox in an Adult.

says: "During a period of twenty years in which the writer has been occupied in studying eruptive disorders, not a single instance has occurred in which varicella appeared after the fifteenth year."

The statements of these various observers would lead one to regard chickenpox in adult life as a great rarity. We grant that adult varicella is not an every-day occurrence, but that it is not of excessive rarity is evidenced by the fact that within eighteen months we have seen no less than 16 cases in the city of Philadelphia. During the period from 1870 to 1902 there were admitted into the Philadelphia Hospital for Contagious Diseases 35 cases of adult varicella. Nearly all of these cases were sent into the hospital under the erroneous diagnosis of smallpox. Dr. Welch and one of the authors were enabled to successfully vaccinate all who were not protected by previous vaccination.

In addition to these 35 cases we have seen 5 other cases within the period 1901–1902, the particulars of which we are able to recall.

TABLE OF AGES OF ADULT CASES OF VARICELLA.

Years.		Years.	
18	2	31	1
19	3	32	3
20	5	34	3
21	2	35	2
21	2	36	1
22	3	38	2
23	1	39	2
24	3	40	1
25	4	42	1
26	1	43	1
27	2	48	1
28	1		—
30	4	Total	51

Of these patients, 32 were males and 19 females; 22 were negroes and 29 were whites. We have also seen a number of cases of varicella between the ages of ten and eighteen years, but these have not been included in the above table.

The history of a patient admitted into the smallpox wards some few months ago is of interest. An unvaccinated man, aged thirty-one years, was sent into the hospital with the diagnosis of smallpox; he was found to be suffering from a curious papular and purpuric eruption of undetermined origin. He was immediately vaccinated on both arms and on the leg. The vaccinations were all successful, but at the end of ten days he fell ill and developed about a half dozen variolous lesions. He was discharged from the hospital about ten days later. About a week afterward he developed at home a fairly extensive eruption of chickenpox. It was evident that this had been contracted in the hospital from a man suffering from varicella who was sent in as a case of smallpox, and who was placed in a separate ward with the above-mentioned patient about a week before the latter's discharge. It is interesting to note that this patient successively passed through attacks of cowpox, smallpox and chickenpox.

The underestimated frequency of chickenpox in adults is further attested by the figures which Wanklyn[1] presented of the cases of varicella sent to the diagnosing station of the Asylums Board of London during the smallpox epidemic of 1901–1902. Of 200 cases of chickenpox which were seen, 16.7 per cent, or 33 cases, were over eighteen years of age.

There are certain features of adult varicella which deserve mention, inasmuch as they are not common in chickenpox in children.

It is not rare for adults to feel ill a couple of days before the appearance of the varicellous eruption. There may be malaise, chilliness, headache and some backache, nausea and moderate rise of temperature to 101° or 102° F. These symptoms are similar to those observed in smallpox, but are less severe. High fever, intense backache, repeated vomiting and prostration are absent in chickenpox. Every now and then one will see cases of varicella in adults in which quite indurated papules will be observed on certain parts of the body. It is particularly on the thick skin of the forehead that these are seen. Typical varicellous vesicles, however, will be found elsewhere upon the cutaneous surface. A significant sign in many of these cases is the presence of vesicles here and there which have undergone rapid rupture and crusting, with the production of a blackish or bluish-black scab and depressed in the center; the borders of these lesions are still vesicular. They present the appearance of having been excoriated by scratching.

COMPLICATIONS AND SEQUELÆ OF CHICKENPOX.

Varicella is one of the least dangerous of the various exanthematous diseases, both as regards mortality and liability to complications. Nevertheless, a sufficient number of rare complications has now been recorded to show that the affection is not entirely devoid of danger to life. Most of the complicating conditions result from infection of the skin at the site of the varicellous vesicles.

It is extremely common for the partially dried vesicle to spread upon the border in the form of flat pustules; or blebs of considerable size may be formed which dry into yellowish friable crusts. These spreading pustules may attain the diameter of a silver half dollar. This peripheral extension is due to infection of the lesion with the pyogenic organisms commonly found upon the skin, and might appropriately be designated *impetigo varicellosa*. Most well-marked cases of chickenpox show some lesions which become the seat of impetigo. This secondary infection is not nearly as pronounced as is seen in smallpox; in severe cases of the latter disease an extensive *impetigo variolosa* almost invariably occurs.

Trousseau[2] states that in an epidemic of chickenpox which prevailed in the Necker Hospital the fever ceased when the malady began, and

[1] Brit. Med. Jour., July 5, 1902.

[2] Page 137.

during from fifteen to forty days *pemphigoid blebs* appeared on different parts of the body, leaving, on the surfaces which they had occupied, ulcerations exactly like those of pemphigus, which ulcerations continued for six weeks or two months.

The "sores" so frequently seen in chickenpox, particularly when the lesions are scratched, represent impetigo lesions. When these sores are numerous a moderate elevation of temperature (101° to 102° F.) may develop and persist for several days.

As a result of this same infection the neighboring glands may become enlarged and in rare cases undergo suppuration. *Boils* and *subcutaneous abscesses* may occur as a result of pyogenic infection. These are not infrequently seen upon the scalp, although any portion of the cutaneous surface may attacked.

Erysipleas.—Erysipelas has been reported as occurring after chickenpox. Freyer[1] speaks of a case of erysipelas migrans complicating varicella, and Holt[2] states that he has known of "3 fatal cases of chickenpox resulting from erysipelas, beginning about the pocks." When we remember that erysipelas is a not uncommon complication in smallpox, it is not surprising that it should occasionally occur in varicella.

Pyemia.—A remarkable case of pyemia resulting from staphylococcic infection through the varicella lesions is reported by Brunner.[3] The child had a suppurative inflammation around the elbow-joint, followed by a double parotitis and abscess of the left middle ear, ending fatally on the ninth day. Autopsy disclosed the presence of pus in the anterior mediastinum, the pericardium, the bronchi, the spleen and the kidneys. The Staphylococcus pyogenes was recovered from the blood, pus and urine during life.

Lohr also records a death from chickenpox resulting from mixed infection with the Staphylococcus pyogenes aureus.

Disseminated Gangrene.—Literature contains numerous references to a serious complication of chickenpox which was called by Hutchinson *varicella gangrænosa*. We have purposely avoided this name in the caption inasmuch as this gangrenous condition is not to be regarded as a variety of varicella or even as a complication peculiar to this disease. It may occur also in vaccinia, variola, scarlatina, typhoid fever and in various pustular dermatoses; it is true, however, that it most commonly complicates varicella.[4]

In mild cases but one or several varicellous lesions may undergo necrosis; in more extensive cases many of the vesicles become involved. The vesicle may either become converted into a bleb, the gangrenous process beginning beneath this epidermal elevation, or the vesicle may dry into a dark crust and enlarge upon the periphery. Upon removal of the crust a sharply marginated, punched-out, freely discharging

[1] Deutsch. med. Wchnschr., 1878, **4**, 111. [2] Loc. cit.

[3] Quoted by Brown: Varicella, Twentieth Century Practice of Medicine, 1898.

[4] An excellent description of this affection is given by Crocker under the title of Dermatitis Gangrænosa Infantum, Textbook of Diseases of the Skin, American edition, 1903, p. 535.

ulcer is seen. A dusky-red areola surrounds the ulcer or eschar. In extensive cases the temperature rises to 104° or 105° F., and the patient rapidly sinks. Lung complications, particularly pulmonary infarction, are common. Mild cases of gangrene may recover. The affection is most common in debilitated infants, more especially those in whom the varicella is preceded by some other illness. In Griffith's case the chickenpox was preceded by measles, diphtheria and pneumonia.

Cases of gangrenous varicella have been reported by Hutchinson, Demme, Abercrombie, Andrew, Crocker, Büchler, Jamieson, Löwenhardt, Payne, Stanifooth, Haward, Vierordt, Griffith, Lockwood, Silver, Woodward and others.

We have, on several occasions, observed localized gangrene occurring at the site of smallpox pustules; these cases all terminated fatally. Stokes,[1] of Dublin, reports a case of vaccinia gangrænosa ending in recovery.

Synovitis and Arthritis.—Synovitis and arthritis have been reported as rare complications. Laudon[2] and Perret[3] have both published examples of joint involvement in chickenpox. The patient of the former, a boy, aged four years, developed high fever early in the course of varicella, followed by marked swelling of the left elbow-joint. Recovery took place after several weeks.

Semtschenke, quoted by Rille, saw 2 cases of purulent pleurisy and purulent arthritis in an epidemic of chickenpox in Russia.

Högyes reports a case of varicella in a girl, aged seven years, followed by nephritis and subsequently by an inflammation of several joints, accompanied by high fever and ending in recovery.

Braquehaye saw a purulent arthritis of the knee and elbow develop on the ninth day of a varicella which was apparently running a normal course. Despite incision and drainage death resulted. On autopsy a septic endocarditis was also discovered.[4]

Marfan and Halle[5] described 2 cases of serous *involvement of the larynx* through the presence of varicellous vesicles. In one case, in a boy, aged three years, tracheotomy was performed, the patient recovering. In the other, a child, aged nine months, with a well-marked chickenpox, developed stridor and dyspnea; diphtheria bacilli were absent. Bronchopneumonia and diarrhea supervened and death resulted; the post-mortem examination revealed the presence on the right vocal cord of a round, shallow ulcer, evidently the remains of a varicella vesicle.

Nephritis.—Nephritis is one of the most serious of the complications and sequelæ of varicella. While it occurs in only a very minute percentage of cases, there are in the literature a sufficient number of recorded instances to cause physicians to keep in mind the possibility

[1] Dublin Jour. Med. Sci., June, 1880. [2] Deutsch. med. Wchnschr., 1890, **16**, 567.
[3] Province méd. Lyon, 1889, **3**, 256.
[4] Quoted by Brown: Twentieth Century Practice of Medicine.
[5] Quoted by Brown: Ibid.

of its development and to watch the kidneys in the treatment of this otherwise trivial disease.

Henoch[1] was one of the first to mention nephritis as a complication and reported 4 cases following chickenpox. Janssen,[2] Högyes,[3] Oppenheim,[4] Brunner,[5] Unger,[6] Rille,[7] Schwab, von Jürgensen[8] and Dillon Brown[9] have all described similar cases.

The nephritis usually comes on during the first or second week of the disease. It varies in severity as does this complication in other infectious diseases. In severe cases an abundance of albumin and tube casts may be present in the urine. As a rule, the nephritis is mild, recovery taking place promptly. Dillon Brown, however, reports a case in which the kidney involvement after a mild attack of varicella ran a chronic course, ending fatally some ten years later. Högyes' case terminated fatally through complication with pneumonia, and Rille reports an uncomplicated nephritis ending in death and showing on autopsy parenchymatous changes in the kidneys.

Bronchitis and Bronchopneumonia.—Bronchitis and bronchopneumonia are mentioned as complications by Meigs and Pepper, and Rille report a peculiar form of pleuro-pneumonia ending fatally on the nineteenth day after varicella.

Nerve Complications.—De Toni[10] reports a meningeal syndrome in a girl, aged three and a half years, after a severe attack of varicella. Five weeks after recovery the patient developed a right-sided ophthalmoplegia.

Winnicott and Gibbs[11] describe a case in which paralysis of the limbs, drowsiness and later difficulty in swallowing and in articulating and transient squinting developed during an attack of typical chickenpox of moderate severity. The child made a good recovery, and showed no sequelæ. The author reviews other cases of nervous system complications in chickenpox, which are of rare occurrence. Eight of these were cases of encephalitis, 2 myelitis and 2 meningismus. None of these cases was fatal. In spite of the severe immediate signs and symptoms, no residual sign or mental change has been reported. This is unlike epidemic encephalitis lethargica.

Krabbe[12] reports a case in which symptoms of myelitis developed after a rather mild attack of chickenpox with typical eruption. There was difficulty in walking, with ataxic gait, pain in the extremities,

[1] Berl. klin. Wchnschr., January, 1884, No. 2.
[2] Nederl. Tijdschr. v. Geneesk., 1884, **20**, 223.
[3] Orvosi hetil., Budapest, 1885, **29**, 11.
[4] Berl. klin. Wchnschr., December 26, 1887.
[5] Aerztl. Mitth. a-Baden, Karlsnute, 1888, **42**, 49.
[6] Wien. med. Presse, 1888, **29**, 1449.
[7] Wien. klin. Wchnschr., 1889; Deutsch. med. Wchnschr., 1891.
[8] Varicella, Nothnagel's Encyclopedia of Medicine.
[9] Varicella, Twentieth Century Practice of Medicine.
[10] A Case of Serous Meningitis Following Chickenpox: Riv. di clin. ped., 1924, **22**, 346.
[11] Varicella Encephalitis, Brit. Jour. Child Dis., 1927, **23**, 107.
[12] Varicella Myelitis, Brain, 1925, **48**, 535.

stiffness of the neck; the knee-jerks were at first exaggerated, later absent, the abdominal reflexes absent; the lower limbs were hypesthetic and analgesic. The patient gradually improved and finally recovered completely. Cases of myelitis due to chickenpox are very rarely reported; the author reviews one other case very similar to his own; other cases are reviewed that are regarded by the physicians reporting them as probably polyneuritis or peripheral paralysis following varicella, but which the author considers are more probably a myelitis or encephalo-myelitis; in addition cases of encephalitis following chickenpox are occasionally reported.

Galli[1] reports 2 cases, a boy, aged five years, and a girl, aged two years, brother and sister, in whom a lesion of the cerebellum supervened, due to the varicellous infection, with a syndrome of acute cerebellar ataxia. Both patients made a good recovery, after about two weeks, without sequelæ of any kind.

Waldman[2] reports a case in a woman, aged thirty-two years, in whom, during convalescence from a mild attack of chickenpox with but slight fever, an acute ascending myelitis developed, with sudden loss of power and rapid development of complete anesthesia, retention of urine and feces, followed later by rectal incontinence, flaccid paralysis and trophic ulcerations. The patient lapsed into coma and died "with exhaustion of the vital centers."

Ratner[3] describes a case of chickenpox in a boy, aged four years, in which sudden *blindness* developed nine days after the onset. The child remained totally blind for six days, after which time he began to perceive light and rapidly regained normal vision. At the time of blindness there was no lesion of the outer eye. Ophthalmoscopic examination of the eye-grounds showed a marked pallor of the left disk and a marked congestion and swelling of the right disk; the pupils were widely dilated and immobile. The author finds only 2 other cases recorded in literature in which optic neuritis followed chickenpox. These cases he considers as a type of retrobulbar neuritis of toxic origin. The prognosis is favorable, although some pathological condition of the optic nerve may persist.

Association of Chickenpox with Other Exanthematous Diseases.—It is not at all uncommon for varicella to develop during convalescence from other acute exanthematous disease, such as measles, scarlet fever, smallpox, etc. On the other hand, these diseases may develop in patients suffering from varicella. It is rather rare for these eruptive diseases to be synchronously present in their acutest stages; usually the second disease appears as the first is beginning to decline.

Chickenpox repeatedly broke out in the diphtheria and scarlet-fever wards of the old Municipal Hospital. Under these circumstances the

[1] Nervous Complications of Varicella: Two Cases of Acute Cerebellar Ataxia, Pediatria, 1925, **33**, 681.

[2] Acute Ascending Infectious Myelitis Following Chickenpox, Jour. Am. Med. Assn., 1925, **85**, 1612.

[3] Transitory Blindness after Chickenpox, Med. Clin. North America, 1925, **9**, 809.

varicella would naturally appear not earlier than the end of the second week of the original disease. We have often seen varicella appear in scarlet-fever patients who were profusely desquamating. We have also observed these two diseases present at the same time with vaccinia.

Chickenpox may appear during convalescence from smallpox. The following outbreak of chickenpox among 33 children convalescent from smallpox is of interest.

In November, 1900, a child suffering from chickenpox was sent into the Municipal Hospital of Philadelphia, under the erroneous diagnosis of smallpox. The true character of the disease was recognized and the child vaccinated. This patient did not contract smallpox, but succeeded in transmitting varicella to a number of other children in the ward. These in turn infected new patients as they arrived, and in this manner varicella remained in the children's ward for a period of three months. In all, 33 children suffering from smallpox were attacked. It should be stated that a much larger number of children escaped infection. Whether this was due to temporary insusceptibility or to their having previously had chickenpox, it is impossible to say. The attacks were in the main mild and the accompanying eruption moderate in extent. Inasmuch as the patients were exposed during the eruptive period of smallpox, the chickenpox eruption did not appear until after the variolous lesions had become crusted or were disappearing. The earliest onset of varicella was in a girl, aged seven years, who developed chickenpox on the seventeenth day of the variolous outbreak. In this patient the firm, compact, crusted lesions of smallpox appeared in strange contrast with the recent dewdrop-like vesicles of chickenpox. The patient's temperature had not yet reached normal but was hovering about 100° F. at the time of the appearance of the chickenpox eruption. It then rose to 102° F., subsiding rapidly to 100° F., and in a few days again rising to 103° F., owing to the development of an abscess. In this child the two diseases may be said to have existed simultaneously.

The chickenpox efflorescence appeared in most of the patients from the twentieth to the thirty-fifth days of their smallpox eruption. As the majority of these children entered the hospital on the third or fourth day of the variolous eruption, it is seen that many of the patients did not contract chickenpox for about a month after they were exposed. Inasmuch as the period of incubation of varicella is about fourteen to eighteen days, seldom longer than three weeks, this observation would suggest that during the early eruptive period of smallpox many of the children were not susceptible to the infection of chickenpox. To generalize, we should say that most of the little patients received the infection of varicella during the desiccative stage of smallpox or at about the end of two weeks of the smallpox eruption.

Coincident Smallpox and Chickenpox.—Smallpox and chickenpox may actually exist at the same time. Trousseau states that Delpech published a paper in 1845 in which he reported the simultaneous presence in

a child of the eruptions of chickenpox and smallpox. We have seen one such case ourselves, the attendant circumstances of which leave no doubt as to the correctness of the diagnosis. S. F., a girl, aged five years, developed an eruptive disease which was regarded by a physician as suspicious; thereupon two other physicians independently visited the patient and pronounced the disease to be chickenpox. The lesions dried up in the usual time, but two weeks later the girl became ill and developed typical smallpox.

Thirteen days after the above patient was first seen a smaller sister, aged two years, developed the eruption of chickenpox. Twenty-four hours later the characteristic lesions of smallpox appeared upon her. It is to be noted that this child was exposed to the smallpox infection at the same time as her sister. On admission to the hospital the little patient was covered with firm variolous papules. The face, arms and legs were profusely involved, the trunk to a lesser extent. Upon the forehead near the border of the hair were two crusted and superficially ulcerated varicella lesions. A half dozen or more varicellous lesions were also observed upon the back and a few on the abdomen and chest. Upon the lower portion of the back was a comparatively recent chickenpox vesicle just beginning to dry. The subsequent course of the case left no doubt as to the variolous nature of the second eruption. Two other children of this family who were protected against smallpox by previous vaccination showed crusted varicellous lesions upon different portions of the body.

THE PATHOLOGY OF CHICKENPOX.

The Skin.—Unna excised a characteristic "chickenpox" lesion from a boy, aged eight years, on the second day of its existence. The following description is condensed from Unna's detailed findings:

In contrast with the central depression in the variolous vesicle the vesicle of varicella is tent-shaped, with the central point at the summit. The lateral walls rise obliquely from a broad base toward the roof, which is formed by a few stretched, horny scales. From these cellular partitions radiate downward as in smallpox. The chickenpox lesion is consequently divided like the smallpox lesion, but the point where the septa join lies not in the center of the base but in the covering or roof. The cavity proper only occupies the upper part of the much-widened prickle layer. It is limited beneath by the deeper strata of the prickle layer, which show pathological changes. In the center the cavity extends downward to the papillæ of the corium, which are swollen and enlarged and which project into the cavity. The roof of the vesicle is formed by the original horny layer with the addition of a few layers of flattened transitional epithelium.

The degenerative changes in the cells of the rete mucosum are typically represented in varicella, and can be better studied in this

disease than in variola, for in the latter affection the onset of suppuration obscures the process. The early pus formation and the slowness of the process are the chief features which distinguish the cavity formation in smallpox from that in chickenpox. Extensive *fibrinoid metamorphosis* of the epithelium takes place as in variola. The varicellous process commences with the *reticulating* liquefaction of a few prickle cells of the central and upper prickle-cell layer, in the middle of the first appearing congestive spot. The completely liquefied, confluent cavities rapidly dilate to form the vesicles; the persistent unliquefied epithelium is compressed to form the septa, as are the cells above to form the cover. While this septate cavity chiefly enlarges by swelling upward, the *ballooning* colliquation proceeds in all of the epithelial cells of the base, especially at the center of the pock, then at the lateral margin, and in all of the healthy epithelial cells of the center.

Many of the colliquated cells assume the form of peculiar giant cells. Even the septa which run through the vesicle are frequently surrounded by ballooned giant cells. At the base of the chickenpox lesion the balloons form a loosely connected covering which runs over the central papillary apices, often only in a single layer. The contents of the vesicle, at the height of its development, consist of finely granular or coagulated fibrin, enclosing a few fibrinously degenerated, compressed or ballooned epithelia and almost no wandering cells. The cutis shows a marked dilatation of the bloodvessels, a moderate serous saturation and a considerable enlargement and multiplication of the cells about the vessels; the emigration of white corpuscles is reduced to a minimum.

Notwithstanding its appearance, the vesicle of chickenpox is not unilocular. The absence of resultant scarring is due to the superficial position of the pock, the non-occurrence of suppuration, and the early repair by young epithelial cells.

Blood.—Engel,[1] in 1897, noted an eosinophilia in this disease after the second day which in one case reached as high as 16 per cent. Hoffmann[2] states that the changes are similar to those found in variola but less pronounced, characterized by high lymphocytosis with a corresponding reduction of the number of polymorphonuclears, high increase of eosinophiles, presence of myelocytes and changes in the Arneth index lasting about twenty days. In variola he found the number of leukocytes highly increased for weeks, whereas in varicella there were normal or only slightly increased from the eighth to the tenth day. Changes in the erythrocytes and hemoglobin were slight and of no significance. Bunting and Thewlis[3] also found the changes similar to those in mild smallpox but much less marked. Mitchell and Fletcher[4] state the average leukocyte count tends to be increased from

[1] XV Congres für Innere Medicin, 1897.
[2] New York Med. Jour., 1923, **118**, 616.
[3] Arch. Path. and Lab. Med., 1926, **1**, 194.
[4] Jour. Am. Med. Assn., 1927, **89**, 279.

1000 to 3000 cells above the normal according to age, even in the first day of the rash. They could find no change in the differential count consistent enough to be of significance in diagnosis.

THE DIAGNOSIS OF CHICKENPOX.

Smallpox.—Chickenpox may usually be distinguished from smallpox without much difficulty. In exceptional instances, however, the diagnosis may present perplexities which may cause even a physician experienced in these diseases to delay in pronouncing definitely as to the nature of the disease. Errors may occur through regarding a mild smallpox as chickenpox, or looking upon a severe varicella as variola. The points of differential importance are as follows:

FIG. 84.—An unusually sparse smallpox eruption in an unvaccinated child; vesicles firm and prominent.

1. **The Vaccinal Condition of the Patient.**—If a child under five or six years of age presents an eruption which exhibits features both of chickenpox and of smallpox, the presence of a typical vaccinal cicatrix would constitute strong presumptive evidence against the variolous nature of the exanthem, for successfully vaccinated children of this age do not acquire smallpox save under extraordinary circumstances. The same evidence would obtain in an adult successfully vaccinated within a similar period of time.

2. **Initial Symptoms.**—The appearance of the smallpox eruption is preceded by two or three days by an illness characterized in its most complete form of chills, fever, headache, backache, vertigo, nausea and vomiting, prostration and general pains. The more severe the oncoming eruption, the more pronounced are these symptoms apt to be. The syndrome is often incomplete, the invasive illness presenting but a few of the above-mentioned symptoms. In exceptionally mild

cases one may not be able at all to elicit a history of a prodromal stage. It is extremely uncommon, however, for this to occur, and the existence of premonitory symptoms should always be regarded as a matter of great differential importance.

Except for occasional malaise a half day or so before the appearance of the chickenpox eruption, there is in the vast majority of cases no prodromal stage. We had the opportunity in the Municipal Hospital of studying an outbreak of chickenpox among convalescents from scarlet fever. The continuous temperature records show that in nearly every case the eruption appeared before any pyrexial elevation occurred. Occasionally in adults chickenpox may, however, be preceded by a prodromal illness suggestive of, but milder than, that observed in smallpox. These patients seldom experience vomiting or prostration and the febrile elevation is, as a rule, moderate.

FIG. 85.—Chickenpox eruption; vesicles easily broken, leaving abraded bases.

3. **Constitutional Symptoms.**—The fever and prostration in the eruptive stage are usually more severe in smallpox than in chickenpox. This is not an invariable guide, however, as severe cases of varicella are accompanied by higher temperature than very mild cases of smallpox.

4. **Distribution of the Eruption.**—It is a well-known and important fact that the smallpox eruption attacks with predilection the face and distal portions of the extremities. Upon the trunk, and especially the abdomen, the lesions are nearly always more sparse. In chickenpox the eruption is usually most profuse on the trunk, particularly the back, and relatively sparse on the wrists, hands, feet and face. In general, it may be stated that smallpox prefers the exposed surfaces and chickenpox the covered.

It has been stated that chickenpox does not attack the palmar and

plantar surfaces. This statement is erroneous, inasmuch as the palms of the hands and soles of the feet are every now and then attacked in pronounced cases. Of course, one never sees such a profusion of lesions in these regions as is observed in smallpox.

5. **Extent of the Eruption.**—The number of lesions upon the skin should not be regarded as important evidence. An unvaccinated child admitted into the Municipal Hospital had but 5 lesions upon the entire cutaneous surface. On the other hand, a lad with chickenpox occupying a different ward had about 1400 lesions and another boy over 3000.

6. **Character of the Lesions.**—In smallpox the eruption begins as firm papules, which slowly increase in size and develop into vesicles and pustules. Not all variolous papules are shotty, but they are more deeply seated and have a more infiltrated base than the chickenpox lesions. The variolous vesicles are often harder than the papules. They are moderately uniform in size, and are often, although by no means always, umbilicated. The vesicles are multilocular and difficult to rupture with the finger-nail.

Chickenpox lesions may begin as maculo-papules, but within a few hours some become frankly vesicular. The epidermal roof is thin and easily broken, permitting the exit of a clear, watery serum. With the collapse of the vesicle the infiltration seems to disappear and a superficial excoriation is often left. The vesicle is often unilocular, but little diagnostic value should be placed upon the comparative degree of evacuation of variolous and varicellous vesicles with a needle. Chickenpox lesions vary greatly in size, some being as small as a millet seed and others as large as a finger-nail. They do not become umbilicated save by central caving in or desiccation. The early drying, with the production of a depressed, blackish crust in the center and irregular puckering of the vesicle or pustule on the periphery, is highly characteristic of chickenpox.

It is not rare in an extensive eruption of varicella to find one or several vesicles which resemble variolous vesicles, and, on the other hand, in smallpox to occasionally see a few superficial vesicles which resemble those of chickenpox.

7. **Manner of Eruption.**—The eruption of smallpox comes out without interruption in the course of twenty-four to forty-eight hours. The lesions show, therefore, a quite uniform development. (It should be remarked, however, that the eruption on the face is always a little in advance of the development elsewhere.) The chickenpox eruption comes out in crops or successive or alternate days, and the lesions may be seen in varying stages of development. The coexistence of recent tense vesicles, older puckered vesico-pustules and dried crusts is highly characteristic of the disease.

8. **Course of the Eruption.**—Smallpox lesions undergo a gradual evolution from papule to crust in the course of ten to twelve days (in modified cases five to six days). Chickenpox lesions last from two to four

days and then crust. The crusts of smallpox are dense and compact, while those of chickenpox are thin and friable. The presence of numerous hard, mahogany-colored crusts embedded in the horny layer of the palms and soles bespeaks smallpox.

There is no one characteristic symptom on which a differential diagnosis between smallpox and chickenpox can be based. The case is to be viewed in all its aspects and a diagnosis made from the history and the associated local and constitutional manifestations. A due sense of proportion should be exercised in attributing proper weight to the presence and absence of the various symptoms. Even when this is done there are occasional cases in which twenty-four hours' delay and observation are desirable in order to definitely establish the diagnosis.

Impetigo Contagiosa.—If chickenpox is seen after the desiccation of the vesicles the disease may be confounded with impetigo. Indeed, impetigo is commonly engrafted upon a varicella, in which event the lesions spread upon the borders in the form of a vesicular ring. Impetigo contagiosa is characterized by the formation of vesicles or blebs which rapidly become pustular, rupture and form superficial crusts. The face is the seat of predilection and is usually exclusively affected, although the hands, and in rare cases the trunk, may present lesions. The vesicles are thin-roofed and flaccid, seldom exhibiting the tenseness of varicella vesicles. The patient, as a rule, suffers no constitutional disturbance at all. The mucous membrane of the mouth is exempted. The lesions do not appear, as in varicella, in several crops, but increase irregularly as a result of finger inoculation. The disease is caused by inoculation of the skin with certain pyogenic organisms.

Varicella runs a briefer course and the lesions disappear in a short time without local treatment; the existence of antecedent cases of chickenpox, or the development of later ones, after an interval of two weeks constitutes strong corroborative evidence.

The Relationship of Chickenpox to Herpes Zoster.—Bokay,[1] of Budapest, first drew attention to a relationship between varicella and zoster. In 1892 he suggested that the infection of chickenpox might, instead of producing a generalized eruption cause a herpes zoster. In 1909 he reported 9 further cases apparently corroborating his thesis. Since then a large number of cases, perhaps 150 in all, have been reported in which herpes zoster developed in persons exposed to chickenpox or in a smaller group, varicella from exposure to zoster. Many of the reporters state that the chickenpox subjects had not had any other known exposure. The propositions stated appear to be as follows: (*a*) That herpes zoster in a domicile is followed by one or more cases of varicella; (*b*) that cases of chickenpox in a house may be followed by cases of herpes zoster; (*c*) that occasionally cases of herpes zoster are associated with a generalized outbreak of vesicles, indistin-

[1] Wien. klin. Wchnschr., September 30, 1900.

guishable from varicella, although commonly reported as generalized zoster.

Netter[1] discusses and tabulates the cases reported in French literature. In complement-fixation tests with the serum of chickenpox patients, using material from herpes zoster lesions as an antigen, and with the serum of zoster cases and varicellous material as an antigen, Netter found the reaction definitely positive. He concludes that the same virus may alternately cause varicella and herpes zoster, the former being essentially contagious, the latter only rarely so. The above complement-fixation tests have not yet been adequately confirmed.

Of considerable significance is the observation of Kundratitz.[2] This writer was able to inoculate the skin of children with the contents of a herpes zoster lesion and protect them from varicella despite intimate exposure. The vesicle produced according to such an excellent investigator as Kyrle, is clinically and histologically indistinguishable from the vesicle of chickenpox.

THE PROGNOSIS AND TREATMENT OF CHICKENPOX.

Prognosis.—Chickenpox is, with the possible exception of rubella, the mildest of the acute exanthematous diseases. As Trousseau remarks, patients never die of varicella *per se*, although deaths in rare instances have occurred from complications. Most of the complications which have been recorded have been wound infections—impetigo, erysipelas, abscesses, gangrene, etc. With the exception of the first-named condition, these are extremely rare.

Treatment.—The matter of the isolation of patients with chickenpox is a somewhat mooted problem. Varicella is such a mild disease that it is just a question whether children in good health should not be allowed to take it. Those who reach adult life without passing through the disease are apt to contract it at times under awkward and embarrassing circumstances. When children are weakly or suffering from some other disease they should, if possible, be protected against chickenpox. When isolation is carried out it should be continued until detachment of all the primary crusts.

The constitutional symptoms of varicella are ordinarily so mild as to require no internal treatment. Where there is febrile disturbance children should be kept in bed and upon a bland diet.

The local treatment is of considerable importance. It is well to paint the lesions on the face daily with tincture of iodine diluted with 5 parts of alcohol. This should be continued until they dry. Then

[1] Herpes Zoster and Varicella, Bak. Acad de méd., 1924, **98**, 494; Paris méd., 1924, **50**, 521.

[2] Cited by Kyrle: Histobiologie der Menschlichen Haut, Etc., Berlin, Springer, 1927.

a soothing ointment may be applied. For the body we would recommend the following:

℞—Acidi phenici	3	cc.
Glycerini	8	"
Acidi borici	4	"
Resorcinolis	4	"
Pulv. zinci oxidi	30	"
Aquæ hamamelidis	60	"
Aquæ q.s.	240	"

As has already been stated, some chickenpox lesions are followed by indelible scars; these may be due to an early necrosis involving the papillary layer of the skin, in which event they cannot be prevented. In other cases the scars are due to a slow ulceration, the result of pyogenic infection of the lesions. Scratching is liable to produce scars by infecting the skin. In young children the finger-nails should be closely trimmed to prevent traumatism from scratching; when scratching cannot be otherwise controlled the hands should be enclosed in muslin bags attached firmly about the wrists or in aluminum mits. Doubtless the rare cases of varicella gangrænosa are due to infection of the skin. It is important to keep the hands and the entire body scrupulously clean.

In severe cases it is important to examine the urine to be sure that a nephritis be not present. If the latter complication arises it should be treated upon the usual principles governing the care of this condition.

CHAPTER VII.

SCARLET FEVER.

Synonyms.—Scarlatina: German, Scharlach; French, *la Scarlatina;* Italian, *Scarlattina;* Spanish, *escarlatina;* Latin, *febris rubra.*

Definition.—Scarlatina is an acute specific, infectious disease, due to a special strain of the streptococcus, characterized by a sudden onset with high fever, headache, vomiting and sore throat, followed on the second day by a generalized punctiform rash which later gives rise to desquamation.

There is a tendency to the development of cervical abscess, otitis media and nephritis. One attack usually confers immunity for a lifetime.

History.—The origin of scarlet fever is involved in obscurity; there are many suggestive descriptions in the writings of the later Greek and Roman physicians, but none are sufficiently complete and explicit to warrant the conclusion that they referred to scarlet fever.[1]

Some writers have believed that certain passages in the works of Hippocrates referred to scarlatina, but inasmuch as no mention was made by this careful observer of the most conspicuous symptom of this disease, namely, the exanthem, it may be accepted that the references in question pertained to another malady (in all probability diphtheria).

Gregory[2] says that scarlet fever "probably invaded the world soon after measles and smallpox made their debut, for the Arabian physicians describe a species of measles which, from the extent of the desquamation, we may be assured was scarlatina."

Not until the sixteenth century is reached do we find convincing descriptions of scarlet fever. Ingrassias, of Palermo (1560), depicted this disease and was the first to properly differentiate it from measles.

THE ETIOLOGY OF SCARLET FEVER.

Historical Review.—It is now practically certain that scarlet fever is caused by a hemolytic streptococcus, called Streptococcus scarlatinæ. However, this discovery has been made by no single individual alone, but by a number of investigators who have helped to formulate the fabric of proof.

Of course, the infectiousness of scarlet fever has led many to attempt

[1] For the history of scarlet fever see work of Noirot (Histoire de la scarlatine, Paris, 1847).

[2] Eruptive Fevers, New York, 1851, p. 146.

its experimental transfer to human beings and the lower animals by inoculations with material from the fauces and with the blood or scales of skin of scarlet-fever cases, but, as stated by Hektoen,[1] it is doubtful if any of the alleged successful results are scientifically acceptable prior to the work of the Dicks in 1923.

Since 1884, when Loeffler showed the frequency of hemolytic streptococci in scarlet fever, it had been universally recognized that they bore an important etiological relationship to the disease. This view was strengthened by the success of Moser's antistreptococcus (scarlatinal) serum in the treatment of the disease in 1902 and by the toxic reactions and successful vaccination work of Savchenko, in 1905, and of Gabritchewsky, in 1907, with vaccines of scarlet-fever streptococci. When Dochez and Sherman,[2] in 1919, showed by means of agglutination and protection tests that the hemolytic streptococci of scarlet fever were immunologically specific types for the disease and capable of producing an experimental infection of guinea-pigs bearing some resemblance to scarlet fever, the way was prepared for the work of the Dicks,[3] who, in October, 1923, inoculated the throats of 5 volunteers with a culture of scarlet-fever streptococcus and produced a mild form of the disease in 1. Of 5 additional volunteers inoculated in the same manner with a filtrate of the culture none contracted the disease, although one of these subsequently inoculated with the organisms themselves developed a mild attack of what was regarded as scarlet fever.

Since the toxin had been already demonstrated by Dochez and others, the Dicks prepared and injected small amounts of sterile toxin into the skins of individuals who had never had scarlet fever and observed that about 45 per cent yielded positive reactions. Among scarlet-fever convalescents however, the reactions were negative and the results interpreted as indicating the presence of specific antitoxin developed during the course of the disease. When in 1924 they[4] showed that a volunteer giving a positive skin reaction passed through a mild attack of scarlet fever following inoculation of the tonsils with a culture of Streptococcus scarlatinæ, whereas a second volunteer giving a negative skin reaction did not contract the disease, the evidence seemed quite conclusive that Dochez was right in his hypothesis that scarlet fever was an infection of the upper respiratory tract or some other tissue with a specific streptococcus and that the rash and other lesions were due to the action of its toxin.

This work has been confirmed by Nicolle, Conseil and Durand,[5] who have recently described the development of scarlet fever—with characteristic fever, angina, glossitis, eruption and desquamation—in a person inoculated with the fourth subculture of a streptococcus isolated from the throat of a scarlet-fever patient. This streptococcus

[1] Jour. Am. Med. Assn., 1923, **80**, 84.
[2] Ibid., 1924, **82**, 542.
[3] Ibid., 1923, **81**, 1166.
[4] Ibid., 1924, **82**, 301.
[5] Arch. d' l' Inst. Pasteur (Tunis), 1926, **15**, 229.

was hemolytic, did not ferment mannitol and produced a toxin demonstrable by skin tests with the culture filtrates. Furthermore, the person inoculated had previously shown susceptibility to scarlet-fever toxin by a positive reaction (local erythema and slight rise of temperature) to an intradermal injection of unfiltered urine from the scarlet-fever patient. Other persons were tested with the urine, and 2 who gave positive reactions to filtered urine were later proved susceptible to scarlet fever.

This was further substantiated by the preparation by Dochez of an antiscarlet-fever serum by the immunization of horses with living Streptococcus scarlatinæ and the demonstration by Blake and others of its curative activity in the disease followed by the preparation of an antitoxin by the Dicks by the immunization of horses with the toxin alone. When it was shown that the injection of these sera into the skins of scarlet-fever patients caused a blanching of the erythema similar to the effects produced by injections of scarlet-fever convalescent serum first demonstrated by Schultz and Charlton in 1918, it appeared certain that the rash at least was due to the action of the toxin of Streptococcus scarlatinæ and particularly since Trask and Blake[1] demonstrated the presence of the toxin in the blood and urine of scarlet-fever patients and found that it was neutralizable by both human convalescent and the Dochez and Dicks horse immune sera.

The evidence of these investigations has led many, probably the majority, to accept Streptococcus scarlatinæ as the real and actual cause of scarlet fever. But others are doubtful of the correctness of this conclusion and believe that they merely afford new and stronger proof of the very important relation of this organism as one of secondary infection, while the real etiological agent is as yet undiscovered. Zlatogoroff and Derkatch,[2] McLachlan[3] and others have reported positive Dick skin reactions with the toxins of alleged non-scarlatinal strains of hemolytic streptococci as well as the preparation of immune sera with them capable of giving the Schultz-Charlton extinction reaction. Bristol,[4] Dabney[5] and Meyer[6] have expressed the view that the rash is merely an anaphylactic reaction to the protein of the streptococcus while others, and especially Caronia and Sindoni[7] and other Italian investigators, regard the diplococcus described by di Cristina,[8] in 1921, as the cause of the disease. That there may be a possible relationship between this organism and Streptococcus scarlatinæ is suggested by Brokman and his co-workers,[9] who observed that of 4 children inoculated with a vaccine of it, the Dick skin test became negative in 2.

[1] Jour. Exp. Med., 1924, **40**, 381.
[2] Jour. Infec. Dis., 1928, **42**, 56.
[3] Jour. Hyg., 1927, **26**, 84.
[4] Am. Jour. Med. Sci., 1923, **166**, 853.
[5] Jour. Am. Med. Assn., 1924, **82**, 956.
[6] Deutsch. med. Wchnschr., 1923, **49**, 509.
[7] Pediatria, 1923, **31**, 745.
[8] Pediatria, 1923, **31**, 1 and 857; 1924, **32**, 1193; Pediatria Arch., 1925, **1**, 3.
[9] Compt. rend. de la Soc. de biol., 1925, **93**, 946.

Streptococcus Scarlatinæ.—Morphologically and culturally this streptococcus cannot be differentiated from other hemolytic streptococci, but differentiation is possible by immunological reactions. For this purpose Dochez and Bliss[1] have employed agglutination and protection tests with specific immune sera while the Dicks[2] have developed a method of differentiation based upon the neutralization of toxin by convalescent scarlet-fever serum or antiscarlet-fever antitoxin produced by the immunization of horses. Tunnicliff[3] employs agglutination and rapid opsonic tests and Rosenow[4] a precipitin test.

The streptococcus has been secured by various investigators not only from the throats of scarlet-fever patients, but likewise from the local wounds and burns of surgical scarlet fever, from the lochial discharges of puerperal scarlet fever and contaminated milk in a milk epidemic of the disease. Furthermore it has been found by Williams and her associates in normal throats, in measles, wounds and other non-scarlatinal conditions which indicates that it may be as widely distributed as the diphtheria bacillus.

Nature of Scarlet Fever.—At the present time scarlet fever is generally regarded as an infection of the upper respiratory tract with specific strains of this hemolytic streptococcus with the local production of toxins, which absorbed into the system, produce the rash and other constitutional symptoms. In these respects the disease is similar to diphtheria, differing from it in the important fact that in scarlet fever the streptococcus itself or other organisms from the naso-pharynx may likewise invade the system and produce local or generalized secondary infections. As shown by Stevens and Dochez,[5] the streptococcus may cause a sore throat without the production of a rash (scarlatina sine exanthemate) not only in susceptible individuals but likewise in those possessing sufficient antitoxic immunity to give negative skin reactions. Indeed, while the scarlet-fever patient may acquire an immunity to the toxin of the organism during an attack of scarlet fever, an antibacterial immunity to the organism itself may not be acquired which probably explains why secondary streptococcus infections are sometimes observed late in convalescence among individuals who possess the antitoxic immunity and give negative Dick skin reactions.

Modes of Transmission.—The germ of scarlet fever is chiefly, if not exclusively, conveyed in two ways: (1) Directly from a scarlatina patient to the newly infected subject, and (2) through the intermediation of infected objects.

The vast majority of cases of scarlatina doubtless result from exposure to persons suffering from the disease and to carriers of the organism. Some maintain that the disease cannot be *conveyed by a third*

[1] Jour. Am. Med. Assn., 1920, **74**, 1600; Bull. Johns Hopkins Hosp., 1920, **31**, 173; Jour. Exper. Med., 1922, **36**, 575.
[2] Jour. Am. Med. Assn., 1925, **84**, 802.
[3] Ibid., 1927, **87**, 625.
[4] Ibid., 1926, **86**, 9.
[5] Ibid., 1927, **87**, 2137.

person, but the clinical experience of numerous careful observers is strongly opposed to such an opinion. Indeed, there are recorded instances of such transmission which appear quite conclusive, but experience has shown that the danger is very slight.

The infection commonly clings to objects which have come in contact with the scarlet-fever patient, such as bedding, clothing, books, letters, toys, etc. Numerous instances are recorded in which such articles have apparently transmitted the infection. Both Richardson and Peterson traced cases of scarlet fever to infection transmitted in letters. It is an important matter in infectious disease hospitals that all outgoing mail be thoroughly disinfected.

Mode of Reception of the Scarlatinal Infection.—The scarlatinal virus is ordinarily received into the system through the upper air passages. It would seem that the genital tract in puerperal women and cutaneous wounds may also offer a point of ingress for the infection. But in the vast majority of cases the poison is "breathed in" just as in the other acute eruptive fevers. Whether the virus effects its entrance into the blood in the lungs or at some point along the respiratory avenue is a difficult question to answer. Dowson, in 1893, endeavored to prove that the first and essential localization of the scarlatinal poison was in the throat. Bergé,[1] following this view, maintained that scarlatina is primarily a local tonsillar infection, and that the eruption both upon the cutaneous and mucous surfaces is the result of the action of an erythemogenic toxin generated in the tonsils which is exactly supported by present-day evidence. The author cites a number of cases to show that in puerperal and surgical scarlatina the primary tonsillitis is absent, although the bucco-pharyngeal enanthem may be present.

Pregnancy and the Puerperium.—It cannot be said that pregnancy increases the predisposition to scarlet fever, for, according to Senn, Tourtual, and Trousseau, no case of scarlet fever in pregnant women was observed by them during extensive epidemics of the disease. That scarlet fever is an excessively rare occurrence during pregnancy is evidenced also by the statement of Olshausen that he was able to find only 7 cases in medical literature. When scarlet fever does complicate gestation it is prone to lead to abortion or premature delivery.

Great diversity of opinion is expressed in the extensive literature[2] on the so-called *puerperal scarlatina* as to the real nature of this affection.

The fact is recognized that puerperal septicemia may be attended with a rash which cannot be distinguished from that of scarlet fever. The lying-in woman may develop after confinement either a true *scarlet fever* or a puerperal fever with a *septic scarlatiniform rash*. There can be no doubt that in the past many instances of the latter condition have

[1] Pathogénie de la scarlatine, Paris, 1895, p. 126.

[2] An admirable collation of the literature on this subject is presented by Marcel Durand in a Paris thesis entitled Étude historique et critique sur la scarlatine puerpérale, Paris, 1891, pp. 325.

been regarded as puerperal scarlatina. The differential diagnosis is often extremely difficult. The following points would indicate a puerperal infection rather than scarlet fever:

1. The absence of an epidemic of scarlatina and of any history of scarlatinal infection.

2. The presence of lesions of the genital tract, such as inflammation in and around the uterus. In puerperal infection metritis and peritonitis are more commonly found than in scarlatina after confinement.

3. In puerperal septicemia the rash is often irregular. It may be circumscribed to the lower portion of the abdomen; in some cases it is morbilliform. When it is diffuse and scarlatiniform in character the spread over the body is usually more rapid than in true scarlatina. Occasionally the rash may reappear even as often as seven times, as reported by Lucas-Championnière.

4. The associated symptoms seen in scarlatina are only imperfectly present. Angina is, as a rule, slight or absent; the strawberry tongue is not seen; renal complications are rare and desquamation is usually branny instead of lamellar.

5. The mortality is lower in true scarlatina than in puerperal fever with septic rash.

6. A Dick skin test yielding a *negative reaction* would indicate immunity to scarlet fever and exclude the disease.

7. The injection of antiscarlet-fever serum into an erythematous patch causes a blanching in scarlet fever (see Schultz-Charlton extinction test and is a useful test for differential diagnosis.

In doubtful cases the history of a previous attack of scarlatina in the patient would constitute presumptive evidence against the existence of this disease.

It is important to bear in mind that in certain subjects the employment of intra-uterine or even vaginal irrigations of bichloride of mercury may provoke the appearance of scarlatiniform rashes which may be regarded as septic or may be confounded with scarlatina.

Surgical Operations.—It would appear from occasional epidemics in surgical wards of hospitals (such as that reported by Howse[1] occurring in Guy's Hospital), that the scarlet-fever streptococcus may at times gain entrance into the system through wounds.

Furthermore, it is probably true that persons who have undergone a surgical operation have less resisting power to the scarlatinal infection than healthy persons. This view is held by Thomas, who says: "It really seems as if such persons, in consequence of their general condition possessed a greater susceptibility to the disease."

We have observed 4 cases of scarlet fever after surgical operations. One followed circumcision, 1 an operation for deviation of the nasal septum, 1 an excision of cervical glands, 1 after an operation for pyosalpinx and 1 after a simple tenotomy.

[1] Some account of an epidemic of surgical scarlatina occurring in Astley Cooper Ward in 1878, with Remarks, Guy's Hosp. Repts., London, 1879, **24**, 44.

We have also observed an attack of scarlatina following rapidly upon a *burn*. A colored child was admitted to the Polyclinic Hospital suffering from a deep burn of the face and arm. About twenty-four hours after admission the temperature rose to 105° F. and a scarlatiniform rash appeared upon the body. Nothing characteristic was observed in the throat or upon the tongue. The diagnosis was reserved, inasmuch as the symptoms might well have been attributed to an intoxication due to the burn. The child was isolated and a special nurse assigned to look after it. In about four days this nurse contracted a well-pronounced attack of scarlet fever.

Two distinct and separable conditions have doubtless been included in the term "surgical scarlatina." There can be no question that some of the rashes developing after operations represent the exanthem of genuine scarlet fever. On the other hand, a certain proportion, doubtless, are toxic or septic scarlatinoid erythemas which are unrelated to true scarlatina.

The diagnosis should never be made upon the eruption alone, for a septic rash may be quite indistinguishable from that of scarlet fever. The general symptoms must be considered and the condition of the throat, tongue, glands, ears and kidneys determined in order to throw the fullest light upon these difficult cases.

The diagnosis of scarlatina is sometimes indubitably confirmed by the unfortunate transmission of the disease to another subject.

Scarlet-fever Infection in Milk and Ice Cream.—The transmission of the infection of scarlet fever in milk has attracted the attention of physicians for some years.

Thomas, wiring in 1875, referred to two epidemics reported by Bell and Taylor in which the dissemination of the disease was ascribed to infected milk. In the latter epidemic one of the first cases of scarlatina occurred in the family of a milkman whose wife milked the cows. The milk was supplied to 12 families, in 6 of which scarlatina appeared in rapid succession, without contact with the milk server, and at a time when the disease was not epidemic. The milk has been kept in a kitchen in which scarlatinous patients had been treated.

From the now extensive literature upon the subject, we may conclude that scarlatina may be conveyed through a contaminated milk supply. The proposition is not proven beyond the peradventure of a doubt, but the chain of circumstantial evidence is so strong as to render this conclusion almost irresistible. It would, furthermore, appear that the milk is contaminated through contact with an individual suffering or convalescent from the disease. The view advanced by Klein that the cows themselves suffer from scarlatina remains unproven and is not generally credited.

That *ice cream* may also disseminate the disease is indicated by a study by Ramsey[1] of an epidemic occurring in Flint, Mich., during

[1] Am. Jour. Hyg., 1925, 5, 669.

July and August, 1924. A rapidly developing epidemic in hot weather, when scarlet fever is out of season, immediately suggested dissemination through some food product. The results of detailed investigations confirmed these suspicions, and definitely fixed the responsibility for the epidemic on an ice-cream maker who continued working while he was clinically a scarlet-fever patient. He made all of the ice cream sold by his company over the week-end of July 26, a pleasant warm Saturday and Sunday, which invited ice-cream consumption. Of the 116 patients, 62, or 53.45 per cent, were attacked within three days of this Sunday, and an additional 36, or 31.03 per cent, during the following week. Milk supplies were found to have no relation to the outbreak.

The Contagiousness of Desquamating Epithelium.—The view has generally been maintained that the infection in scarlet fever persists as long as there is any desquamation. Within recent years the contagiousness of the scales has been seriously questioned.

Millard,[1] in a thoughtful article, challenges the view that scarlatinal desquamation is infectious. The author obtained the opinions of a considerable number of experts whose answers he has formulated as follows: Sixteen gentlemen out of 21 state that: (1) They can adduce no evidence that desquamating epithelium is, *per se*, a source of infection; (2) they consider that too much importance has been in the past attached to desquamation as a source of infection; (3) their experience does not support the popular view that desquamation after scarlet fever is necessarily an indication that a patient is still infectious; (4) they believe that a patient may continue to desquamate for some time after he has ceased to be infectious; (5) they do not believe that it is necessary, in order to prevent the spread of infection, that patients who otherwise are quite ready to leave the hospital should be detained until every visible trace of desquamating epithelium has disappeared.

In conclusion the writer briefly sums up the principal arguments against the supposition that desquamation is infectious as follows: "(1) The absence of evidence supporting it. It is difficult to believe but that if the old supposition were correct strong evidence of it would ere this have been forthcoming, as is now the case with discharges from the nose and ears. (2) The fact that infectivity begins prior to the onset of desquamation and frequently continues long after desquamation has ceased. (3) The fact that scarlet-fever wards, although abounding in desquamation epithelium, are not a danger to neighboring houses. (4) The fact that the proportion of 'return cases' does not appear to be increased among patients sent out from hospital still desquamating. On the other hand, the principal argument in favor of the view that desquamation is infectious is the fact that patients still desquamating, but otherwise apparently free from infection, have frequently been known to convey the disease to others. The whole

[1] The Supposed Infectivity of the Desquamation in Scarlet Fever, Lancet, April 5, 1902.

force of this argument disappears, however, when we consider that patients apparently quite free from infection, and in whom desquamation has entirely ceased have also been known to convey the disease; moreover, patients still desquamating have frequently mixed freely with others without untoward result."

There is much force in the arguments presented above. It is quite probable that during the process of desquamation the infection is not in the scales, but in the pharyngeal, nasal and aural secretions.

As regards *second desquamation*, most observers do not regard it as capable of transmitting infection. There are some apparent cases of transmission of the disease during second and third desquamation, but there is no proof that the scales conveyed the infection.

There is no evidence to indicate that the scarlet fever contagium is disseminated by *aërial transmission*. The immediate vicinity of scarlet-fever hospitals appears to be as free of the disease as other sections of the city. In this respect scarlet fever differs from smallpox, in which disease the territory immediately surrounding the hospital is apt to show a disproportionately large number of smallpox cases.

The following figures are taken from the *Medical and Surgical Reports of the Boston City Hospital*, 1897:

Radius from Scarlet-fever hospital.	Cases.
$\frac{1}{8}$ mile	0
$\frac{1}{4}$ "	68
$\frac{1}{2}$ "	71
$\frac{3}{4}$ "	75
1 "	72
Within 1 mile of the hospital	286
Beyond the 1-mile limit	756

It is seen from the above figures that no cases developed within the $\frac{1}{8}$-mile limit about the hospital.

Our experience at the Philadelphia Hospital for Contagious Diseases would lead us to believe that the striking distance of scarlet fever is extremely limited.

It has been exceedingly rare for families in the immediate vicinity of the hospital to become attacked with scarlet fever, although they have not escaped smallpox.

The fact that scarlet fever is not carried beyond the confines of the hospital walls rather militates against the view of the infectivity of scales, for in a scarlet-fever ward the air contains myriads of minute particles of desquamating epithelium.

Period of Infectivity of Scarlatina.—In discussing this subject we wish to draw a distinction between the duration of infectiousness of the scarlatinal virus within and without the patient. Reference has already been made to the longevity of the virus outside of the human subject. The contraction of the disease from contact with infected objects may constitute a source of error and obscure the proper estimation of the infectious period.

There can be no question that at the very beginning of scarlatina the contagiousness is limited. We have frequently known children, exposed to the disease at the very outset, escape infection only to contract it when reëxposed a number of weeks later. Children who are immediately separated from a case of scarlet fever as soon as it is discovered will frequently remain well; in this respect scarlet fever differs strikingly from measles, in which disease the contagion is extremely active even before the appearance of the rash.

Scarlet fever is highly contagious during the period of eruption and usually for some time following the disappearance of the rash. The view has been generally held that contagiousness persists throughout the entire stage of desquamation, and that the infectious principle is resident in the epidermal scales. As mentioned above, there have always been some dissenters from this view and the doubt as to the contagiousness of desquamating epithelium is becoming more generally entertained.

Scarlet fever is not only contagious before desquamation begins, but not infrequently after it has completely terminated. It is obvious, therefore, that the infection must reside somewhere in the body apart from the cutaneous surface. Experimental and clinical evidence both point to the throat, nose and ears as the probable lurking places of the infectious organisms. It is, therefore, of importance to continue the isolation of patients until discharges from the nose and ears have ceased.

It is probable that the prolonged infectivity manifested by certain cases of scarlatina is due to the presence of the scarlatinal streptococcus in the secretions of the throat or in the nasal and aural discharges.

Stevens and Dochez,[1] for example, found the scarlet-fever streptococcus in the throats of 65 per cent of cases of scarlet fever during the first week of the disease and likewise in the throats of patients at the termination of quarantine (thirty days). They were found most frequently in the throats of convalescents in whom the tonsillar inflammation had not entirely subsided. Nicholls[2] also found Streptococcus scarlatinæ in cultures of the throat of everyone of 40 cases of scarlet fever at the end of the third week. There seemed to be little diminution in the degree of throat infection, as determined by the amount of growth up to the end of the third week, irrespective of the severity of the case, the use of antitoxin or the presence of complications. All strains isolated at the end of the third week were potent toxin producers. Cowie, Parsons and Poncher[3] state that a bacteriophage or lytic principle develops quite uniformly and characteristically in the stools of scarlet-fever patients, seldom in those of chickenpox patients. In scarlet fever the lytic principle was active for Bacillus coli, Bacillus

[1] Jour. Exper. Med., 1924, **40**, 493.
[2] Am. Jour. Hyg., 1927, **7**, 84.
[3] Mich. State Med. Jour., 1925, **24**, 294.

dysenteriæ (Shiga and Flexner), Bacillus typhosus, Bacillus paratyphoid A and B, but had no lytic effect on hemolytic streptococci isolated from the throats of scarlet-fever patients.

It is practically impossible to state just at what period a case of scarlet fever ceases to be infectious. The more remote the time from the onset of the disease, the greater is the likelihood of the infection having been extinguished. Probably for this reason the isolating of the patient for the full period of desquamation has been found to be a good working rule.

Physicians connected with scarlet-fever hospitals not infrequently see patients who have remained in the hospital from eight to twelve weeks, give rise, upon their return home, to other cases in the same household. And this occurs despite the most careful disinfection of the body and the clothing.

These *return cases* occur in the experience of many hospitals in from 2 to 4 per cent of the patients. We have seen patients at the end of eight, nine, ten and eleven weeks, after every vestige of desquamation had disappeared, give rise to the disease in others. In a case observed by us we learned that, after the dismissal of the child from the hospital, the ear began to discharge again; shortly afterward a second case developed in the family.

IMMUNITY AND SUSCEPTIBILITY TO SCARLET FEVER.

One attack of scarlet fever generally confers a lasting immunity, and this fact has been a stumbling block in accepting Streptococcus scarlatinæ as the cause of the disease, because in no other streptococcus infection is lasting immunity so well developed. But this is probably because the toxin of this streptococcus is soluble or exogenous and capable of engendering the production of antitoxin largely responsible for the immunity. A similar situation is noted in erysipelas, but in other streptococcus infections it would appear that immunity is largely antibacterial in nature, which seldom reaches the degree of protection afforded by antitoxic immunity. It is also highly probable that Streptococcus scarlatinæ is widely distributed and that children as they grow up acquire minor infections with it insufficient to produce the disease but with absorption of enough toxin from time to time to engender sufficient antitoxic immunity for protection and responsible for negative Dick skin reactions.

There is no such universal susceptibility of persons to scarlet fever as is known to exist toward measles and smallpox. Experience teaches that but few people enjoy a natural immunity against these latter diseases. Many persons, however, escape contracting scarlet fever even though freely exposed to its infection.

The contagion of scarlet fever is a most *capricious* one; it may repeat-

edly spare an exposed individual and lead him to believe that he is immune against it, only to smite him at some subsequent period.

This *temporary immunity* against scarlet fever has been repeatedly noted by various observers. Nurses have frequently been observed during the closest attendance upon patients suffering from scarlet fever to remain free from infection, and yet later contract the disease. It would appear in these cases that for some reason or other the resisting power of the subject is lowered at the time of infection; this explanation seems to us to be more plausible than the assumption that the attack is determined by an unusually intense infective agent.

In some instances it would appear that the temporary immunity against scarlet fever is overcome by infection through unusual channels. The puerperal state and surgical operations are said to favor the development of the disease.

Von Leube[1] gives an interesting account of an attack of scarlatina in his own person following a wound received in making an autopsy upon a patient who had died of an unusually severe case of scarlet fever. He states that he had considered himself perfectly immune, having been exposed as a child, and having attended any number of cases under all sorts of circumstances. Ten days after the postmortem wound upon his finger he developed sore throat, and on the following day he vomited, had a "decided fever" and the scarlatina rash. The course of the disease was one of medium severity.

The susceptibility to scarlatina *commonly disappears in adult life;* at any rate, many adults who have never had the disease escape infection, although freely exposed. Patients suffering from scarlet fever have on numerous occasions been placed in the wards of general hospitals without appearing to disseminate the disease among other occupants of the ward. Such experiences illustrate the very limited susceptibility of persons who have passed the age of puberty.

During a period of twenty-eight years the students of the various medical colleges in Philadelphia have been conducted through the wards of the Philadelphia Hospital for Contagious Diseases in order to study the various infectious diseases therein treated. Many thousands in all have taken advantage of this bedside instruction. They were taken into the scarlet-fever wards and remained from one to two hours in intensely infected atmospheres. *About one-half of these students,* according to their statements, *had never had scarlet fever,* and yet not a single one contracted the disease. This is strong proof of the frequent abrogation of the susceptibility of adults to scarlet fever.

Age.—Age is a most pronounced factor in the determination of susceptibility to scarlet fever. It is a general experience that infants under one year of age exhibit a lessened disposition to contract the

[1] Specielle Diagnose der inneren Krankheiten, Leipzig, 1893, **2**, 364.

disease; this is still more true of nurselings under six months, and in infants under three months of age scarlatina is excessively rare. The infrequency of the disease at this tender age may be judged by the statements of experienced observers in reference thereto.

Fleischmann[1] saw no cases under six months of age; Eulenberg, none under eight; Thomas, none under five; Böning saw no cases under one year; Senfft saw but 1 patient under one year; Gaupp, only 2; Haller observed 1 case at five months; Voit, 1 at two and a half months; Kupfer, 1 at two months; Veit, 1 at two weeks.

This represents an extremely scant number when the large number of cases of scarlatina observed by these men is taken into consideration. In Johannesen's statistics of scarlet-fever deaths in Norway from 1862 to 1878 the number of infantile attacks is considerably greater. He reports 15 deaths from scarlatina under six months and 93 under one year. In our own experience at the Philadelphia Hospital for Contagious Diseases we have found that among 5000 cases of scarlet fever admitted into the hospital, about 1 per cent consisted of infants under one year of age. We have on a number of occasions had infants a few months old brought into the hospital with mothers suffering from scarlatina, but we have seldom observed them to contract the disease. We have seen them suckle at breasts covered with the scarlatinal rash, draw a febrile milk, and yet remain perfectly well.

The question whether there is a *congenital scarlatina* is most difficult to answer. Children are so commonly ushered into the world with a red rash that but little reliance can be placed upon the existence of an exanthem. Furthermore, it is not uncommon for the tender epidermis of the infant to peel off after some days and thus cause a desquamation. Baillou, Ferrario, Stiebel, Hüter and others saw infants that were alleged to have scarlatina at birth (most of them being born of mothers suffering from scarlet fever at the time), but the facts do not appear to us to warrant the unreserved acceptance of the diagnosis. Murchison saw 2 pregnant women with scarlet fever, and in each case the child born at the time was free of the disease. Elsässer also saw a healthy babe born of a mother with scarlatina.

Children from two to five years of age appear to be most susceptible to the contagium of scarlatina. From five to ten years the attack-rate is somewhat less, and after the period of puberty is reached the susceptibility to the disease is greatly lessened. No age, however, appears to guarantee absolute immunity against scarlatina inasmuch as persons even over the age of ninety-five have been known to contract the disease.

Murchison's valuable statistics of scarlet-fever deaths in England and Wales, covering the enormous number of 148,829, will give a fairly accurate idea of the incidence of the disease in the different age periods:

[1] Mentioned by Thomas in Ziemssen's Encyclopedia of Practice of Medicine, p. 180.

Under 1 year	9,999 (6.7	per cent)
From 1 to 2 years	20,975 (14.1	")
2 to 3 "	23,842 (16.0	")
3 to 4 "	22,528 (15.1	")
4 to 5 "	17,726 (11.9	")
5 to 10 "	38,591 (25.9	")
10 to 15 "	8,676 (5.8	")
Total under 5 "	95,070 (63.8	")
From 5 to 15 "	47,267	
15 to 25 "	3,871	
25 to 35 "	1,306	
35 to 45 "	671	
45 to 55 "	331	
55 to 65 "	185	
65 to 75 "	88	
75 to 85 "	30	
85 to 95 "	4	
Over 95 "	6	
	148,829	

It will be seen from the above tables that considerably over one-half of the deaths of scarlatina occurred in children under five years of age. Almost 90 per cent occurred in those under ten years, and over 95 per cent under fifteen years of age.

These figures correspond very closely with statistics of scarlet-fever deaths in Berlin from 1875 to 1891, and with Johannesen's statistics for Norway. As showing the fatal cases in children under one year the latter statistics are of particular interest:

Fatal Cases of Scarlatina in Christiania Under One Year of Age (Johannesen).

First month	0
Second to third month	3
Fourth to sixth month	12
Seventh to twelfth month	78

The above deaths were out of a total of 1040 fatal cases.

Family Predisposition.—Some families, at times, exhibit an unusual susceptibility to scarlatina; this is manifested not only by several members of the family contracting the disease, but likewise by the severity of the attack. Thomas[1] recognizes "an intense family predisposition, showing itself by numerous and severe attacks in the family as soon as one infection has taken place in it." Trousseau says: "Scarlatina epidemics may be full of danger for an entire population, or they may assume this character only for a single family. The malignancy limits itself in a measure to a single hearth, and in such cases the disease is malignant for all persons that live within its circle." Henoch[2] expresses much the same idea; he says: "Striking to me appeared the fact that if scarlatina breaks out in a family, very frequently also a second and third child are taken off under similar conditions, and in this way whole families can die out."

Copeman,[3] during a severe epidemic of scarlet fever in 1844, saw 4

[1] Loc. cit., p. 175. [2] Vorlesungen über Kinderkrankheiten, 3d ed., p. 654.

[3] Jahresbericht, etc., der Gesammten Medicine, R. Virchow and Aug. Hirsch, vi, Jahrgang, 1871, **2**, 247.

children in a family die so suddenly that poisoning was suspected; a fifth child went through an ordinary attack of scarlet fever.

A somewhat similar instance has come under our observation. In the winter of 1902 we saw a family in which 4 children were smitten with scarlet fever. All fell suddenly ill with vomiting, which was attributed by the mother to free indulgence in candy. Soon the scarlatinal rash manifested itself. The oldest daughter, aged seventeen years, died in five days; a second one had a temperature of 105° F., with intense prostration, and recovered, as did a third child, only after a most desperate illness. The infection in these cases was most virulent, and yet the prevailing type of scarlatina in the city at that time was quite mild.

These severe family epidemics are difficult to account for. Henoch presupposes a mixed infection in such cases. Thomas does not seek an explanation in an unusually intense infection, for he says "the infecting cases are frequently of a mild character."

Epidemics of this character are happily uncommon. In some instances there is a tendency to family immunity, the members thereof exhibiting an almost complete insusceptibility to the disease.

Season.—Hirsch has studied the seasonal incidence of 435 epidemics of scarlet fever occuring in Norway, Sweden, Russia, Germany, Holland, France, Italy, Spain and North America. Most of the epidemics occurred in autumn, as will be seen from the following figures: autumn, 29.5 per cent; winter, 24.7 per cent; summer, 24 per cent; spring, 21.8 per cent.

In England, since the days of Sydenham, it has been recognized that scarlatina prevails most in the fall; 55,956 deaths in London from scarlatina during a period of twenty-four years gave the following percentages; autumn, 35.54 per cent; winter, 23.85 per cent; summer, 22.75 per cent; spring, 17.87 per cent.

In the *United States* scarlatina is most prevalent during the *latter part of winter* and during the *early spring* months. The vital statistics for 1870 show the largest number of deaths in March. The first five months of the year exhibit a considerably greater mortality than the rest of the year:

Scarlatina Deaths by Months in the United States in 1870.

January	2,205	September	927
February	2,393	October	1,000
March	2,726	November	1,281
April	2,294	December	1,705
May	2,146	Unknown	5
June	1,326		
July	1,216	Total	20,320
August	1,096		

Arranged according to seasons, the figures read as follows:

Spring	7166	Autumn	3208
Summer	3638	Winter	6303

According to Murchison, epidemics of scarlet fever in France occur more frequently in the spring and summer months.

Johannesen classifies as follows 65,785 cases of scarlet fever occurring in Sweden from 1867 to 1878:

	Per cent.		Per cent.
January	11.3	July	6.6
February	9.2	August	6.3
March	9.1	September	5.7
April	7.8	October	8.0
May	7.8	November	10.4
June	6.9	December	10.7

It is seen that the greatest number of cases occurred in November, December, and January.

In Berlin, from 1877 to 1883, there were 5428 deaths from scarlatina, with the following monthly mortality:

	Per cent.		Per cent.
January	6.7	July	8.0
February	5.3	August	8.5
March	5.8	September	10.7
April	6.1	October	13.8
May	7.0	November	10.9
June	8.1	December	8.5

The greatest number of deaths occurred in autumn, September, October and November, the maximum being reached in October.

From the various statistics presented it is seen that season apparently has some influence on scarlatina prevalence. The same months in different countries show, however, widely divergent figures.

The different character of the climate in the countries mentioned may account for the discrepancies in the monthly morbidity incidence. It will be necessary to carefully compare the climatic and meteorological conditions by month in the various countries before anything can be definitely said as to the influence of season upon the spread of scarlatina.

Influence of Urban and Rural Localities.—As would be naturally expected, the prevalence of scarlatina is greater in city than in country districts. This is to be accounted for by the more extensive intercourse between cities and by the greater crowding and more intimate contact of the people. The vital statistics of the United States for the year 1900 show a very distinct difference between the city and rural death-rate by months:

Death-rate from Scarlatina by Months in Cities and Rural Districts per 1000 of All Deaths.

	Cities.	Rural.
January	1.6	0.8
February	1.8	0.9
March	1.5	0.9
April	1.4	0.8
May	1.4	0.7
June	1.0	0.4
July	0.6	0.3
August	0.5	0.3
September	0.4	0.3
October	0.8	0.4
November	0.8	0.8
December	1.2	0.8

Scarlet fever is practically endemic in the great centers of civilization; the disease in the large cities of the world increases and decreases from time to time, but never dies out completely.

Race.—There is strong evidence that *negroes* are *less susceptible* to scarlet fever than the whites, and, furthermore, that the mortality-rate among the former is *very considerably lower* than in the Caucasian race.

Minor, writing in 1875, says: "The total number of blacks dying of scarlet fever in the southern states was 107 out of a total black population of 3,713,327; so that 1 out of every 34,704 of the aggregate black population died of scarlatina. The total number of whites dying of scarlet fever was 446 out of a total white population of 4,811,962; so that 1 out of every 10,790 of aggregate white population died of scarlet fever. It will be at once noticed that the disease is much more frequent among the whites than among the colored population. During epidemics the whites have seemed to be the sufferers, and there is reason to believe that there is a certain immunity from epidemic scarlatina existing among the negroes of the South."

During the Civil War[1] 378 whites took scarlet fever, of whom 70 died, and 118 negroes contracted the disease, of whom but 2 died. Comparing the number of the white and black troops it is seen that the attack-rate was 54 in the black race to 26 in the white; on the other hand, 70 deaths occurred among the whites and only 2 among the negro soldiers.

The United States census of 1870 demonstrated the fact that the foreign-born population of the country was 5,567,229, and that 1 out of every 6105 died of scarlet fever. The population of the native-born whites was 28,120,788, of whom 1 out of every 1473 died of scarlet fever. The negro population was 4,880,009, of whom 1 out of every 16,886 died of the disease.

It is thus seen that scarlet fever destroyed, relative to the population, over ten times more whites than negroes. The census statistics of 1850 give somewhat similar results.

The United States census report of 1890 shows a scarlatina death-rate among the whites of 14.2 per 1000 deaths from all causes to 2.7 among negroes. The figures of the 1900 census are almost identical—12 death-rate among the whites as compared with 2.6 among the blacks. These statistics would indicate that the Caucasian race in the United States is six times more susceptible to scarlatina than the negroes.

Osler states that the natives of India enjoy a high degree of natural immunity.

The Chinese have been hitherto regarded as enjoying a high natural immunity, but Kuang and Shig[2] in a recent survey have stated that the incidence of scarlet fever in China shows that the disease is practically absent or very mild in South China, not unduly severe in Shanghai

[1] Medical and Surgical History of the Rebellion, Part I, vol. **3**.
[2] Nat. Med. Jour. China, 1924, **10**, 153.

and central provinces and severe in the north. The disease seems to be comparatively more frequent among westerners residing in the country. In the north, although several deaths have been recorded among them, infection is usually not so severe as among the same classes of Chinese. The special virulence of the disease manifested when Chinese are attacked in epidemic form may be explained partly by its recent introduction into the country before any natural immunity is yet evolved.

Toyoda and his colleagues[1] have observed 37.3 per cent positive Dick reactions among 11,284 Japanese with 80.9 per cent for children aged three years, which indicates that this race does not have a higher natural immunity than the white races. Zoeller,[2] however, observed only 8 per cent faintly positive reactions among 50 Anamese. The American Indians seem to have a high degree of natural racial immunity, although Sherwood, Nigg and Baumgartner[3] have found them to yield about the same percentage of positive Dick skin reactions as whites.

Scarlet fever occurs only in human beings as a natural disease. Landsteiner, Levaditi and Prasek[4] claim to have produced it experimentally in the chimpanzee, but not in monkeys; Draper and Hanford[5] also failed to infect monkeys, but Dochez[6] believes that a form of the disease may be produced in guinea-pigs by inoculation with Streptococcus scarlatinæ.

THE DICK SKIN TEST FOR IMMUNITY TO SCARLET FEVER.

Immunity in scarlet fever is believed to be largely due to the presence in the blood and tissues of an antitoxin for the toxin of Streptococcus scarlatinæ. When this antibody is present in sufficient amounts the intracutaneous injection of 0.1 cc. of a high dilution of the toxin is followed by its neutralization and a negative reaction; when absent the injected toxin acts as an irritant and produces a mild inflammatory area known as a positive reaction. A *negative* skin reaction, therefore, indicates immunity to the disease while a *positive* reaction indicates susceptibility.

The Relation of the Dick Test to Immunity in Scarlet Fever.—In diphtheria antitoxic immunity is practically the whole story and the Schick skin test for its detection has proven very reliable and useful, but unfortunately this is not true of the Dick test in scarlet fever because antitoxic immunity is not the only mechanism involved.

In the great majority of individuals giving negative Dick reactions scarlet fever has not developed after exposure to the disease and the

[1] Jour. Orient. Med., 1927, **6**, 6.
[2] Compt. rend. d. la Soc. d. biol., 1924, **91**, 1315.
[3] Jour. Immunol., 1926, **2**, 343.
[4] Ann. d. l'Inst. Pasteur, 1911, **25**, 754.
[5] Jour. Exper. Med., 1913, **17**, 517.
[6] Jour. Am. Med. Assn., 1924, **82**, 542.

antitoxic immunity has sufficed for protection. But individuals have been encountered by Lees[1] and others who developed scarlet fever despite negative Dick reactions and others have escaped the disease upon exposure even though they gave positive reactions and were apparently without antitoxin protection.

Of course the possibility of error in conducting the tests is to be kept in mind and likewise the existence of different strains of Streptococcus scarlatinæ. If the test is conducted with a deteriorated toxin falsely negative reactions may occur as likewise if the toxin is injected under instead of *into* the skin. Or individuals may possess antitoxin for one strain and give negative skin reactions to it while susceptible to the toxin of another strain. In a limited experience we have not observed scarlet fever among negative reactors, but they have apparently occurred in the practice of others. But even if an individual possesses an antitoxic immunity and gives a negative Dick reaction it is possible for the streptococcus to produce scarlatinal angina with or without the rash (scarlatina sine exanthemate). The latter is doubtless of greater frequency than the former because the presence of enough antitoxin in the blood to give a negative Dick reaction is usually sufficient for preventing toxin skin rashes unless the patient is infected with a particular virulent toxin producer.

It would appear, therefore, that antitoxin in the blood sufficient for giving a negative Dick reaction is indicative of an immunity against scarlet fever in the majority of instances. But it may not be sufficient for protecting against local infections of the upper respiratory tract with Streptococcus scarlatinæ and even of deeper infections. Likewise there may be enough diphtheria antitoxin in the blood to give negative Schick reactions but yet such individuals may carry virulent diphtheria bacilli in the naso-pharynx and even show superficial infections but the diphtheria bacillus is not capable of producing deeper and systemic infections as is apparently true of Streptococcus scarlatinæ. Nicholls,[2] for example, has demonstrated the presence of Streptococcus scarlatinæ in a notable proportion of individuals who exhibited features of infection with hemolytic streptococci without evidences of clinical scarlet fever. Some of these had tonsillitis, some acute pharyngitis and others a variety of complications of the respiratory tract. Usually they had been exposed to scarlet fever and as Nicholls points out, an existing immunity to the soluble toxin of Streptococcus scarlatinæ does not necessarily prevent the development of even severe local pyogenic infections with this organism in persons in contact with the disease. Individuals so infected may serve as foci of dissemination and negative Dick reaction is little or no indication that a person exposed to scarlet fever is not liable to pyogenic infection with Streptococcus scarlatinæ but usually without the production of the rash.

[1] Jour. Am. Med. Assn., 1927, **88**, 1133.
[2] Jour. Clin. Invest., 1926, **3**, 411.

PLATE XV

E. F. FABER, DEL.

A Positive Dick Skin Reaction

Of course when positive reactors fail to contract scarlet fever upon exposure to the disease escape may be due to fortuitous circumstances, but it is quite probable that other antibodies and especially opsonins for Streptococcus scarlatinæ may be responsible. This possibility is also suggested by the fact that while some races and notably the American Indians may show the same percentage of positive Dick reactions as whites, yet the incidence of scarlet fever among them is distinctly lower as shown by Sherwood and Baumgartner[1] and suggesting the operation of some immunity factor other than the antitoxin.

Technique of the Dick Test.—The toxin is produced by cultivating Streptococcus scarlatinæ in a broth containing 1 per cent sheep blood for four or five days followed by Berkefeld filtration to remove the organisms and culture tests for sterility. For use it must give a reaction in a susceptible individual in dose of 0.1 cc. of a 1 to 1000 dilution injected intracutaneously. Lower dilutions may be employed but are inadvisable because of the occurrence of pseudo-reactions due to other substances in the broth-culture medium. The diluted toxin is preserved with phenol or tricresol and keeps for several weeks, being much less susceptible to deterioration than the diluted toxin for the Schick test and much more resistant to heat.

The skin of the forearm is cleansed with alcohol and 0.1 cc. of diluted toxin injected *intracutaneously* with a fine needle in exactly the same way as in the conduct of the Schick test described and illustrated in Chapter XV.

A control injection is not ordinarily required after some experience has been gained since pseudo-positive reactions do not occur in more than 1 to 2 per cent of cases in our experience, providing the toxin is prepared with sheep blood broth and used in a 1 to 1000 or higher dilution. But if a control is desired the fluid may be prepared by placing the diluted toxin in boiling water for one hour which destroys the toxin; the dose is 0.1 cc. injected in the same manner.

The reactions must be read in twenty to twenty-four hours because they occur earlier than Schick reactions and do not persist nearly as long.

A *positive reaction* consists of an area of erythema with a diameter of at least 1 cm. or approximately the size of a dime; in the majority of instances the reactions vary in size from a nickel to a quarter or half dollar. There is little or none of the subcutaneous edema so likely to be noted in positive Schick reactions. The erythema is apt to be paler, less well defined (Plate XV) and more apt to be read as negative than the Schick reaction, but in some instances is very well marked and may reach a much larger size. In well-marked reactions a slight rash may be observed in the elbow and tenderness of the axillary glands may occur. But superficial ulcerations and systemic reactions are not to be feared. Sometimes a positive reaction consists

[1] Jour. Immunol., 1926, **11**, 343.

of an area of reddish points in a white background, but the diffuse erythema without edema is the usual reaction; severe reactions may be surrounded by a zone of pallor.

Fading begins almost immediately and in the usual mild reactions does not leave the brownish discoloration or desquamation so likely to be observed in positive Schick reactions.

Incidence of Reactions.—The incidence of positive and negative reactions varies greatly according to age and social conditions and to a lesser extent according to sex and the potency and strain of toxin employed.

Infants under six months of age are apt to yield negative reactions due to placental transmission of antitoxin. After this time the transmitted immunity begins to disappear and children from three to ten years of age yield the highest percentage and most marked reactions.

After six years children begin to acquire immunity probably by reason of clinically undetected infections with Streptococcus scarlatinæ and at fifteen years and up the incidence drops to the level of about 25 per cent for adults.

Children from crowded areas, as in cities and public schools, are much more likely to acquire hidden infection and immunity than children in country districts and private schools and the incidence of positive reactions is, therefore, smaller among the former. Zingher,[1] for example, observed 83 per cent positive reactions among a group of 320 private-school children and but 22.7 per cent among 589 public-school children.

Males usually show a relatively greater immunity and smaller percentage of positive reactions than females, probably because boys mix around more than girls and consequently contract to a greater extent hidden infections with Streptococcus scarlatinæ and acquired immunity. Dyer, Caton and Sockrider,[2] for example, observed 69.6 per cent positive reactions among a group of boys of four to twenty-one years, and 75.7 per cent among girls of the same age and social condition.

Children of the same family have been noted to give similar reactions, as is true also with the Schick test; in case of variations the younger children have usually shown positive reactions and the older negative, the reverse of this being very rare.

An analysis of many thousands of tests by Zingher,[3] Dick and Dick,[4] Colby,[5] Nesbit,[6] Rosen and Korobicina,[7] Silcock,[8] Toomey,[9] Lees,[10]

[1] Jour. Am. Med. Assn., 1924, **83**, 432.
[2] Pub. Health Repts., June 11, 1926, p. 1159.
[3] New York State Jour. Med., 1924, **24**, 915.
[4] Jour. Am. Med. Assn., 1925, **84**, 1477.
[5] Minnesota Med., 1925, **6**, 568.
[6] Jour. Am. Med. Assn., 1925, **84**, 805.
[7] Ibid., 1476.
[8] Lancet, 1925, ii, 1324.
[9] Am. Jour. Dis. Child., 1927, **33**, 197.
[10] Jour. Am. Med. Assn., 1927, **88**, 1133.

Lavan Black,[1] ourselves and others have given the following general percentage of *positive* reactions for all classes:

	Per cent.
0 to 6 months	30
6 to 12 "	60
1 to 2 years	70
2 to 4 "	65
4 to 6 "	60
6 to 10 "	50
10 to 15 "	40
15 to 20 "	30
20 years up	25

But the influence of crowding on acquired immunity is indicated by the fact that among institutional and public-school children of four to ten years the incidence of positive reactions is in the neighborhood of 45 per cent, whereas in private schools with less crowding and in private practice the incidence is in the neighborhood of 75 per cent. The same is true in the case of the Schick reaction, since city children are much more apt to acquire an immunity to diphtheria than children in the rural and less-crowded districts. Zingher has observed that in about 75 per cent of children the Dick and Schick tests agree, but more children are apt to show negative Dick with positive Schick reactions than the reverse.

Among individuals who have had (presumably) scarlet fever the incidence of positive reactions is in the neighborhood of 5 to 10 per cent. The reaction is almost invariably positive during the first few days of the disease, but may be negative as early as the fourth day and almost always by the seventh to the tenth day. In the following years the immunity apparently disappears in some individual which accounts for positive Dick reactions and the well-known clinical fact that second attacks of scarlet fever may occur. During an attack of scarlet fever the rash at the site of a former Dick reaction may become pale, which suggests the presence of a local depot of antitoxin capable of neutralizing the rash-producing toxin.

Mention may be also made of the skin tests conducted by Zoeller[2] with Caronia's filtrates of di Cristina's diplococcus. In a series of 56 individuals positive reactions were observed in 28 per cent, but these were less pronounced than the Dick reactions. In 66 per cent the two tests agreed. DeVilla[3] observed 51 per cent positive reactions among children without a history of scarlet fever and in 4.3 per cent of those who had the disease, but it is not possible to express an opinion of the relationship of the reactions to scarlet-fever immunity.

Practical Value of the Dick Test.—When a comparatively fresh and potent toxin is available the Dick reaction would appear to be a reliable index of immunity and susceptibility to scarlet fever in the majority of instances in so far as systemic infection with the *toxin* of

[1] Jour. Am. Med. Assn., 1927, **88**, 896.
[2] Bull. et mém. de la Soc. méd. d. hôp., 1925, **49**, 485.
[3] Pediatria, 1924, **32**, 665.

Streptococcus scarlatinæ is concerned. But as previously stated, *negative reactors are still subject to local infections with Streptococcus scarlatinæ,* although not apt to develop the rash or other constitutional symptoms. But they may develop pyogenic infections with the organism, be carriers of it and transmit the disease to others. In other words, the presence of sufficient antitoxin in the blood for yielding negative Dick reactions may not be an index of complete immunity to Streptococcus scarlatinæ because antitoxin immunity alone is not the sole mechanism of complete protection in scarlet fever.

Furthermore, the test is not now as popular as formerly for the detection of susceptibility to scarlet fever, because active immunization with scarlet-fever toxin has fallen into disfavor, although the successful vaccination of about 90 per cent of susceptible and positive reactors may be possible if at least five injections of toxin are given as described on page 356. But the absence of a thoroughly endorsed short-cut method of vaccination has detracted from the practical value and widespread application of the Dick test for the detection of susceptibles, although when toxin immunization is practised it is an efficient and satisfactory method for determining whether or not antitoxin has been produced.

But we believe that the test is of value in both private and institutional practice for the detection of susceptibility, since toxin immunization is worth while as discussed below, even though the production of antitoxin may not prevent local infections with Streptococcus scarlatinæ. Furthermore, the fact that the reactions can be read in twenty hours renders it valuable for the detection of susceptible individuals exposed to the disease if it is desired to passively immunize these immediately by an injection of antiscarlet-fever serum or convalescent serum. The high percentage of unpleasant reactions following the injection of antiscarlet-fever serum, however, has induced many physicians and families to take a chance on contracting the disease, and this attitude has reduced the practical application of the test. With convalescent serum, however, this objection does not hold because it produces little or no reaction (page 457).

The test is also of value in the diagnosis of scarlet fever. If *negative* during the first day or two of an exanthem, like that sometimes following the administration of the salicylates in the treatment of sore throat, the individual possesses an antitoxic immunity and scarlet fever can usually excluded in diagnosis. If *positive* the individual is at least susceptible and the rash *may* be of scarlet fever. A positive reaction during convalescence from a disease associated with a scarlatiniform rash would also point against the disease having been scarlet fever.

Furthermore, the test is indispensable for standardizing the antitoxic strength of scarlet-fever serum and for the identification of Streptococcus scarlatinæ and its differentiation from other hemolytic streptococci in doubtful cases of scarlet fever, adenitis, otitis media and the nose and throat of convalescents and contacts in epidemiological investigations.

VACCINATION AGAINST SCARLET FEVER.

Attempts to actively immunize or vaccinate against scarlet fever was begun by Gabritschewsky[1] about twenty-two years ago in Russia, where the disease has always been particularly prevalent and highly virulent. For vaccine he used four-day broth cultures of streptococci from scarlet-fever cases, heated at 60° C. for an hour and preserved with 0.5 per cent phenol. From the description of the reactions which sometimes closely resembled mild attacks of scarlet fever, there is no doubt but that his vaccine contained scarlet-fever toxin in addition to the streptococci and his work anticipated by many years our present knowledge of the etiology and prophylaxis of the disease.

Several Russian physicians used the vaccine on a large scale with the general result that it was considered possible to materially reduce the incidence of the disease by immunization with at least three injections.[2] In the United States the subject was taken up by Watters[3] and Kolmer,[4] and while the latter failed to secure evidence of its prophylactic value in a small series of diphtheria patients in the Philadelphia Hospital for Contagious Diseases, probably because of insufficient dosage, yet he observed that scarlet fever among immunized individuals ran a milder course with a much lower incidence of streptococcus complications.

But this early work never received the attention merited by its importance, probably because the streptococcus was considered but an important secondary organism in scarlet fever. When, however, its status as the cause of the disease was established a few years ago by Dochez, Tunnicliff, the Dicks and others, interest in vaccination against the disease was greatly renewed and especially by the Dicks[5] with injections of the toxin, since active immunization against diphtheria with mixtures of toxin-antitoxin was already on a good basis as a precedent.

Vaccination with Streptococcus Scarlatinæ Toxin.—The toxin is prepared as described above for the skin test and the smallest amount producing a positive Dick skin reaction in susceptible individuals determined and designated as the *skin-test dose*. For vaccination the first dose was originally two hundred and fifty times this amount (designated as "250 skin-test doses") followed by a second dose of 500 and a third of 1000 to 2000 at weekly intervals.

The results were encouraging, but only 30 to 50 per cent of susceptible individuals showed enough antitoxin production to give negative Dick skin reactions and some contracted scarlet fever.

[1] Russk. Vrach, 1905, **4**, 941; 1906, **10**, 469. Centralbl. f. Bakteriol., orig., 1906, **41**, 719 and 844; Berl. klin. Wchnschr., 1907, **44**, 556.

[2] For a complete bibliography of this early work read review by Smith (Boston Med. and Surg., 1910, **152**, 242).

[3] Jour. Am. Med. Assn., 1912, **58**, 546.

[4] Pennsylvania Med. Jour., February, 1912.

[5] Jour. Am. Med. Assn., 1924, **82**, 544; 1924, **83**, 84.

Since then the tendency has been to give larger and larger doses, although the first dose has always been kept at 250 to 500 skin-test doses in order to avoid producing a reaction resembling a mild attack of scarlet fever. Zingher has seen a rash produced by 100 skin-test doses, but this is exceptional and experience has shown that a first dose of 250 is safe for very susceptible individuals (indicated by marked Dick skin reactions) and 500 for those less susceptible. It should be small enough to avoid severe reactions, yet large enough to stimulate the production of antitoxin, so that a larger amount of toxin may be safely given for the second dose. Furthermore, no dose should be out of proportion to the one that preceded it, and if the first has been 500 the second may be 2000, etc. Young and Orr[1] have advised 500, 5000 and 30,000 skin-test doses, respectively, with an interval of *two weeks* between injections, and found that almost 100 per cent of individuals produced enough antitoxin to give negative Dick skin reactions when tested with 1 skin-test dose of toxin and about 64 per cent enough antitoxin to give negative reactions when tested with 10 skin-test doses of toxin.

At the present time the schedule of doses recommended by the Scarlet Fever Committee is as follows:

	Skin-test doses.
Dose 1	500
Dose 2	2,000
Dose 3	8,000
Dose 4	25,000
Dose 5	60,000 to 65,000

In other words, the injection of 3 doses originally advised has been abandoned, but Dick[2] states that the above 5-dose method may be counted on to immunize more than 90 per cent of susceptible persons.

There is nearly always some local reaction at the site of injection consisting of swelling and reddening, which appear within a few hours, and begin to subside in forty-eight hours. The intensity of this local reaction varies with the susceptibility of the person. There may be some desquamation over the area of skin involved.

General reactions, when they occur, usually follow the first dose. They may consist of one or more symptoms, including general malaise, nausea of a few hours' duration and light transient scarlatinal rashes. These reactions begin in a few hours after the injection and subside in forty-eight hours. They occur only in highly susceptible persons, who, if they have a general reaction after the first dose, do not, as a rule, have general reactions after subsequent doses. Lowering the initial dose does not completely eliminate the possibility of these symptoms. None of the reactions are so severe as those that may occur during the course of immunization to typhoid fever or diphtheria. But if improperly graduated doses of toxin are employed severe reactions may follow any dose that is disproportionately large.

[1] Jour. Am. Med. Assn., 1926, **86**, 1340.
[2] Jour. Michigan State Med. Soc., June, 1927.

The full degree of antitoxic immunity is not apparent until one or two weeks after the last dose, although some antitoxin production occurs after the first, and the whole process is more rapid than the production of diphtheria antitoxin by vaccination with toxin-antitoxin mixtures.

It is impossible to state the duration of the immunity, but in most instances it has apparently lasted for several years and gives some promise of being more lasting. In about 2 per cent of individuals it has disappeared within a year after vaccination.

Vaccination with Toxoid and Vaccines.—Naturally attempts have been made under those conditions to shorten the number of injections required and the incidence of reactions after the first dose by converting the toxin into toxoid in order to permit the injection of but 1 or 2 doses with the hope that sufficient antitoxin will be produced for protection without local or general toxin reactions.

Zingher[1] has tried the addition of liquor formaldehyde to a purified toxin as suggested by Glenny and Hopkins,[2] which would appear to be yielding encouraging results in the toxoid vaccination against diphtheria (see Chapter XV), but the results reported by Zoeller[3] and others have not been very encouraging.

However, the method of Larson, Huenekens and Colby[4] is more promising, since they prepare a vaccine of broth cultures of Streptococcus scarlatinæ, containing both the cocci and toxin as originally employed by Gabritschewsky except that the toxin is detoxified by the addition of *sodium ricinoleate* (castor-oil soap). One *intramuscular* injection of 1 cc. is given to young children while older children and adults receive an initial dose of 0.5 cc. followed a week or ten days later by a second dose of 1 cc., because of higher resistance to immunization. The reactions are said to be of a mild character and immunity has been observed as early as eight days after injection. Larson has reported that from 77 to 97 per cent susceptible individuals have been immunized to the extent of giving negative Dick skin reactions; encouraging reports have also been published by Perkins and Megrail,[5] Colby[6] and Lees,[7] but it is still too early to express a final opinion on its value. In our experience the incidence of antitoxin production during the past year has not been as high as observed after the injection of the 5 doses of toxin mentioned above, although we believe that the principle of vaccinating with the streptococci in addition to its toxin is the correct one.

Nitkin[8] still advocates immunization with Gabritschewsky's vac-

[1] Jour. Am. Med. Assn., 1924, **83**, 441.
[2] Brit. Jour. Exper. Path., 1923, **4**, 283.
[3] Comt. rend. Soc. d. biol., 1925, **92**, 144.
[4] Jour. Am. Med. Assn., 1926, **86**, 1000
[5] Ohio State Med. Jour., 1926, **22**, 599.
[6] Jour. Am. Med. Assn., 1927, **87**, 919.
[7] Ibid., **88**, 1133.
[8] Ibid., **87**, 2143.

cine and has observed the incidence of scarlet fever reduced from 16 to 1.4 per cent. Polotevkova,[1] Beresneff,[2] Popoff,[3] Strossner[4] and others have likewise advocated its use and in general terms have observed a reduction in incidence from 7 to approximately less than 1 per cent.

Sindoni,[5] Lazzarini,[6] Piatelli,[7] Caronia,[8] Pichezzi[9] and others have reported favorably upon immunization with vaccines of di Cristina's diplococcus, but it would appear that the results have not been as good as obtained in this country with the toxin of Streptococcus scarlatinæ and we have had no personal experience with them.

Practical Value of Vaccination in Scarlet Fever.—Two factors have weighed more or less heavily against the practical value of active immunization against scarlet fever, namely: (*a*) That antitoxin production alone is not sufficient for absolute protection; (*b*) that the injection of at least 4 or 5 doses of toxin are required. It is true, however, that with antitoxin in the blood sufficient for yielding negative Dick skin reactions the great majority of individuals apparently escape scarlet fever in its clinically recognizable forms, although local infections with Streptococcus scarlatinæ may occur and especially of the upper respiratory tract. It is possible, however, that immunization with the cocci and toxin would improve the immunity and in our opinion this mixed type of vaccination is highly desirable.

But the necessity for 4 or 5 doses practically prevents vaccination upon a large scale as a public health measure, and the outcome of further experiences with 1 or 2 doses of detoxified vaccines or toxins will be eagerly awaited, since the establishment of such a method would go far toward encouraging widespread vaccination as a public health measure.

But even as the matter stands today we believe that the 5-dose method is well worth while in the immunization of *susceptible* individuals most likely to come in contact with scarlet fever as physicians, nurses and the inmates of institutions, particularly for children. Also in private practice for the immunization of children and adults too, when scarlet fever is epidemic or exposure eminent. Under these circumstances the first dose should not be more the 250 skin-test doses, in order to avoid producing a reaction with rash which may be mistaken for scarlet fever; the second dose may be also of 250 followed by 500, 2000, etc., for a total of 6 doses.

In children up to six years of age the Dick skin test may be omitted because of the high incidence of positive reactions, but in older children and adults it should be done first in order to spare the needless immunization of negative reactors and, indeed, our own practice is to conduct

[1] Russk. Vrach, 1921, **11**, 1183.
[2] Prophylaktiches. Med., 1925, **4**, 12.
[3] Ibid., 45.
[4] Deutsch. med. Wchnschr., 1926, **62**, 1470.
[5] Pediatria, 1924, **32**, 241.
[6] Policlinico, 1925, **32**, 595.
[7] Ibid., 1924, **31**, 586.
[8] Pediatria, 1925, **33**, 337.
[9] Policlinico, 1925, **32**, 594.

the test on all children over three years of age and to immunize only the positive reactors.

In families where a case of the disease has developed it is useless and inadvisable to vaccinate, since the first dose may temporarily increase susceptibility and the time is too short anyhow for effective immunization. In such instances the Dick test should be done and passive immunization by the injection of antiscarlet-fever serum or convalescent serum conferred if the immediate protection of positive reactors or susceptibles is desired.

THE SYMPTOMATOLOGY OF SCARLET FEVER.

Period of Incubation.—By the period of incubation is meant the time elapsing between the reception of the scarlatinal poison into the system and the first manifestation of symptoms of the disease. It is well to bear the fact in mind that the reception of the contagion is not invariably coincident with the exposure to the disease.

The breeding stage of scarlatina is briefer and at the same time more variable than that of the other acute exanthemata. Within its comparatively narrow limits a considerable degree of variation occurs. The incubation stage of smallpox, although extending over a longer period, is strikingly uniform and reliable; to be sure, there are some variations, but these constitute exceptions. Measles, too, has a comparatively constant period of incubation.

The various writers on scarlet fever, in giving expression to their views as to the duration of the incubation stage, are guided largely by their individual experiences. Apart from actual differences in the clinical experiences of physicians, some of the widely divergent incubation periods may possibly be attributed to differences in the discriminating judgment of the observers. The more conservative writers are in general agreed that the most common period of incubation of scarlet fever is *between three and seven days;* the narrower these limits are contracted as a general proposition, the greater is the liability to error. Thomas regards "four to seven days as the most frequent interval," and looks upon shorter or longer periods as exceptions to the rule. Von Leube and Forchheimer both subscribe to this estimate. Vogl believes that the exanthem appears three or at most five days after infection.

While these intervals cover the vast majority of cases, there have been recorded occasional authentic instances of much shorter and longer periods of incubation.

Trojanowsky, Förster, Sörensen, Murchinson, Alonzo Clark, Raven, Hagenbach-Burkhardt and others have recorded periods of incubation of twenty-four hours or even less; so that it may be accepted that in rare cases the infection may give rise to symptoms almost immediately after entrance into the system.

As to long periods of incubation, there is much divergence of opinion.

Veit claims it may be twelve to fourteen days; Pasch published a case in which it was twelve days; Gerhardt and Reinhold credited periods of eleven to thirteen days. Bawy records an instance of twenty-one days and Trojanowsky one of twenty-eight days.

Murchison, in his wide experience, has only been able to collect a series of 13 cases in which he could be sure of the incubation period; in not a single one of these cases was the period longer than six days.

On the other hand, Hagenbach-Burkhardt[1] reports 57 cases in which he has been able to study the incubation period. Of this group the remarkable number of 35 had incubation stages of over seven days. Under eight days there were 4 cases; nine days, 2 cases; ten days, 1 case; eleven days, 5 cases; twelve days, 1 case; thirteen days, 4 cases; fourteen days, 2 cases; fifteen days, 5 cases; seventeen days, 2 cases; eighteen days, 1 case; nineteen days, 2 cases; over twenty days, 6 cases. This is certainly a most remarkable array of long incubation periods to come within the experience of any one observer.

Some of these instances and others exhibiting long periods of incubation may possibly be explained upon the grounds of a temporary immunity retarding the susceptibility to the scarlet-fever poison. While unprotected individuals are almost invariably susceptible to the contagion of smallpox and measles, the same is not true of scarlet fever. Certain individual conditions about which little is known seem to make some persons immune at one time and susceptible at another to the infection of scarlet fever.

We have had the opportunity of watching a protracted epidemic of scarlet fever in a home for children in this city. For a period of over three months children contracted the disease two or three at a time and were sent to the Philadelphia Hospital for Contagious Diseases. About 40 out of 100 were thus gradually attacked. It would seem that in many of the children the individual susceptibility was temporarily in abeyance or that the infection was not received by them in the beginning in sufficiently intense or concentrated form.

It is alleged by some writers that a virulent contagium may shorten the period of incubation, and that a similar abbreviation of this stage may result when the scarlatina occurs in a surgical or puerperal subject.

Holt[2] has tabulated records of the incubation period in 113 cases, some of which were observed by him, but most of which have been abstracted from the literature of the subject:

INCUBATION PERIOD.

	Cases.		Cases.
24 hours	6	7 days	8
2 days	15	8 "	2
3 "	28	9 "	5
4 "	25	11 "	1
5 "	6	14 "	1
6 "	15	21 "	1

[1] Ueber Spital infectionen, Jahrbuch für Kinderheilk., vol. **24**, 105.
[2] Diseases of Infancy and Childhood, New York, 1896, p. 889.

It is seen that in 87 per cent of these cases the incubation period was between two and six days.

Simple, Usual, or Normal Scarlatina (Scarlatina Simplex).

Period of Invasion.—During the stage of incubation no symptoms, as a rule, are present, the morbid process being entirely latent. The onset of the disease is sudden. The earliest symptoms are indisposition, fever, headache, vomiting and sore throat. Chills are usually absent except in severe cases. In children *vomiting* is the earliest as well as the commonest of the invasive symptoms, and is, therefore, of suggestive diagnostic import. Not infrequently children in the full bloom of health are quite suddenly seized with vomiting rapidly followed by the other symptoms of scarlatina. Billington observed this symptom in about 80 per cent of his cases. We have obtained a history of the occurrence of emesis in 76 out of 155 cases, or about 50 per cent. We believe that the average frequency of this symptom is greater than would be indicated by these figures. The evacuation of the contents of the stomach may be accompanied by diarrhea, although usually the bowels are constipated. In severe cases in infants convulsions are not uncommon. There is loss of appetite and the tongue is furred. Adults and older children who are able to appreciate the sequence of the symptoms often indicate sore throat as the first.

Temperature.—The temperature rises rapidly, often reaching 102° to 104° F. or more in the course of a few hours. The pulse increases in frequency and, compared with the temperature, is often disproportionately rapid. The radial pulsations may number in children 140 to 160 per minute and in adults 120 to 140.

Headache and vertigo are common, and the patient may be alternately somnolent and restless. The thirst is often intense. The patient is greatly prostrated and presents the facies of a very sick person. The skin is hot and dry, the eyes dull and listless and the face flushed.

The fever in scarlatina is subject to great variations, being influenced by the severity of the epidemic and the nature of the accompanying complications. The pyrexial curve is by no means as constant as is seen in the other two important exanthematous diseases—smallpox and measles.

Wunderlich[1] gives the following as the average febrile course: The temperature at the onset of the disease rises rapidly, and after a few hours reaches 104° to 105° F. or higher. With slight morning remissions the fever still increases from the appearance of the eruption until its complete diffusion over the surface. When the eruption has reached its height the temperature begins to decline by gradual steps, with slight evening exacerbations.

It is thus seen that the fever is a continued one during the invasive

[1] Eigenwärme in Krankheiten.

and early eruptive period and that the pyrexia subsides by lysis concurrently with the fading of the exanthem.

In well-pronounced cases of what might be called the normal form of scarlet fever the early rise of temperature is seldom below 104°, and it not infrequently reaches 105° or 106° F. The high temperature persists ordinarily for four or five days and then a decline sets in.

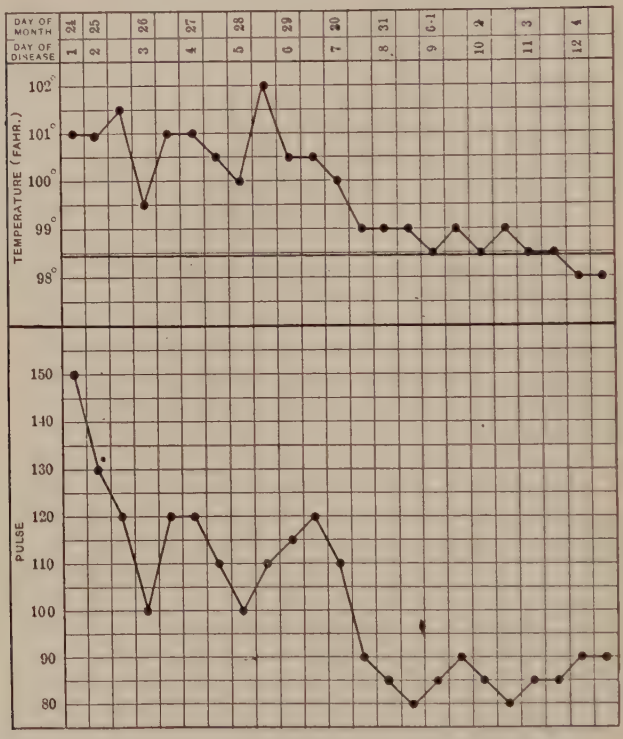


FIG. 86.—Temperature and pulse record of scarlatina simplex. J. B., aged six years; mild case of scarlet fever terminating in recovery.

The intensity and the duration of the fever depend much upon the type of the prevailing epidemic. We determined the duration of the fever in 265 cases of scarlatina which we treated in the winter of 1902–1903, at which time the type of the disease was distinctly mild. Temporary rises of temperature occurring late and resulting from recognized complications or sequelæ were not considered.

It will be seen from the table on p. 363 that in the largest number of cases the fever terminated upon the *sixth* day of the disease. In 158 cases, or 60 per cent, the fever lasted from five to nine days. It must be remembered that the prevailing form of the disease was mild and the mortality low.

DURATION OF FEVER IN 265 CASES OF SCARLET FEVER TREATED AT THE PHILADELPHIA HOSPITAL FOR CONTAGIOUS DISEASES.

Lasting.	Cases.	Lasting.	Cases.
1 day	2	15 days	5
2 days	3	16 "	4
3 "	17	17 "	3
4 "	19	18 "	1
5 "	32	19 "	2
6 "	40	20 "	3
7 "	35	21 "	0
8 "	29	22 "	0
9 "	22	23 "	1
10 "	14	24 "	0
11 "	14	25 "	8
12 "	10	26 "	1
13 "	4		
14 "	4	Total	285

Jamieson states that of 200 cases observed by him the maximum temperature was reached—in 11 cases on the first day, in 76 on the second day, in 75 on the third day, in 36 on the fourth day and in 2 cases on the fifth day.[1]

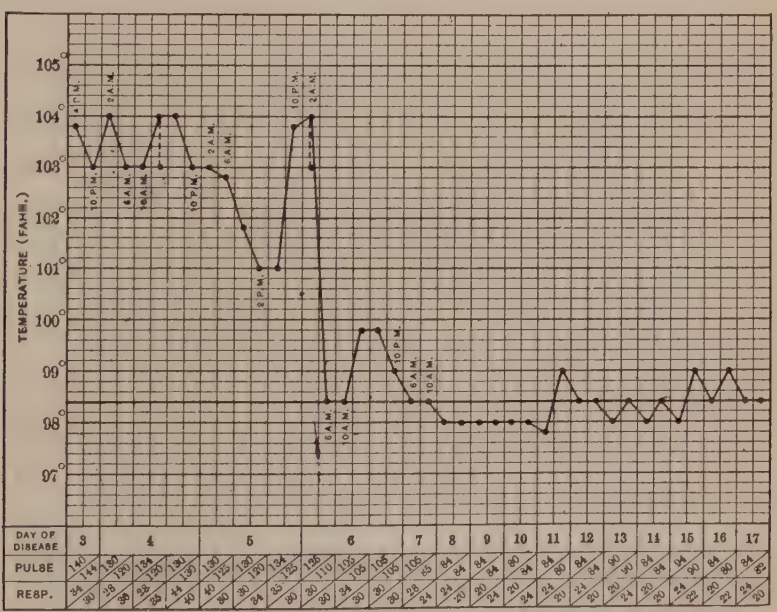


FIG. 87.—R. B., aged seven years; case of scarlet fever with an intense rash and severe early symptoms, terminating rather unusually by crisis.

Deviations from the pyrexial curve above mentioned not infrequently take place. Instead of declining by lysis the temperature may fall by crisis. On the third or fourth day a sudden decline of the fever to

[1] Quoted by Forchheimer: Loc. cit.

normal or subnormal may take place. The temperature may then continue for some days at or slightly above normal. Henoch, Fürbringer and Jürgensen have described such cases and Litten has reported instances of high initial fever followed by an apyretic course. Henoch noted 4 cases out of 175 with normal morning temperature and evening elevation. Litten observed similar cases.

Ordinarily, high fever accompanies severe cases with well-marked eruptions, but there are numerous exceptions to this rule. Leichtenstein mentions a case with marked delirium and intense eruption running an almost afebrile course. Cases of a malignant type may be entirely unaccompanied by elevation of temperature, and, indeed, the temperature may even be below the normal line.

It is not rare for very mild cases to be *unaccompanied by pyrexia*. We recall an afebrile case developing in the hospital whose temperature record we were enabled to observe for several days before the attack.

Furbringer[1] describes a *secondary fever* in scarlatina that is independent of and unaccompanied by any discoverable complication.

Wunderlich, quoted by Trousseau, observed a considerable elevation of temperature during the stage of desquamation. Gumprecht and Jürgensen have also recognized this secondary fever. Thomas[2] describes irregular cases of scarlatina with protracted fever. He writes: "When the fever is irregular it fails to defervesce after the normal progress and disappearance of the eruption and angina, but continues for weeks, sometimes with the same intensity and a typhoid character like that of a variety of scarlet fever presently to be described; sometimes with increasing intensity, especially if it is to prove fatal, and at other times it declines gradually as in protracted defervescence. In such cases the pulse is often very rapid, the heart's action violent and the first sound of the heart diffuse or even replaced by a distinct murmur." And, again, "Not infrequently there occurs still another form of the disease in which there are not only local affections of moderate, perhaps even trifling importance, but also disproportionately severe fever of long duration which characterizes this variety as a typhoid scarlatina." Thomas remarks that in these cases the fever is the chief symptom and that it may be protracted for weeks.

Hyperpyrexia is more frequently observed in scarlet fever than in the other exanthematous diseases. It is not so rare for 107° F. to be reached; such cases usually terminate fatally, although when the hyperrexia is not protracted recovery may take place. In rare cases the fever may mount to an extraordinary height. Wunderlich records a temperature of 110.3° F.; Thomas, 111.2° F.; Leichtenstein, 109° and 109.9° F. and Dr. Currie, according to Gregory, 112° F. These rises of temperature were, as might be expected, shortly followed by death.

Throat Symptoms.—Throat symptoms are, as has been stated, early complained of by adults. On inspection, general faucial redness is

[1] Realencyklopädie, **10**, 472; quoted by Jürgensen: Loc. cit.
[2] Loc. cit., pp. 254 and 269.

observed, involving particularly the uvula, tonsils and soft palate. When the cutaneous eruption begins to manifest itself the redness increases and there develops edema and swelling of the mucous tissues. At times a thin, grayish or yellowish film of exudate may be seen on the swollen tonsils. Often the soft palate, uvula and buccal mucous membrane show a punctated redness similar to that later observed upon the skin.

The stage of invasion is brief, not lasting ordinarily more than twenty-four hours. In some cases the eruption appears before twelve hours have elapsed.

In a series of 84 cases of scarlatina, Barthez and Rilliet observed the eruption appear as the first symptom in 4; in the majority of the cases, however, the eruption manifested itself at the end of twenty-four hours. Trousseau saw a severe case of scarlatina with marked brain symptoms in which the rash was delayed until the eighth day. It is, however, distinctly exceptional for the stage of invasion to last much longer than twenty-four hours.

Stage of Eruption.—The exanthem of scarlet fever usually begins upon the neck and subclavicular regions, then spreading rapidly to the chest, face, abdomen, arms and legs. A variable time elapses in different cases before the acme of the eruption is reached. The milder efflorescences reach their height earlier than those of greater intensity. In severe cases the rash may take until the third or fourth day before its greatest intensity is attained.

The *color* of the scarlatina exanthem varies in different individuals and is extremely difficult to depict in words. It has been variously designated by writers as scarlet, bright red, boiled-lobster tint, raspberry-juice color, rose colored, wine colored, etc. These terms are permissible because they convey a definite impression to the mind, but when these tints are compared with the exanthem at the bedside the terms are seen to be inaccurate. The color of any inflammatory eruption is due to the blood appearing through the texture of the skin. The amount of blood in the skin as determined by the caliber of the cutaneous bloodvessels, the character of the blood and the complexion of the individual all influence the coloration. It is a matter of daily observation that the rash in fair-skinned persons is brighter than in those of swarthy complexion, whose skin contains a greater amount of epidermal pigment. In general, the scarlatinal rash is reddish, sometimes bright, but more often *dull or dusky red*. Sometimes the eruption is so brownish-red, particularly in dark-complexioned individuals, as to almost approach a bright terra-cotta color. More rarely the element of blue is so well marked, particularly in dependent areas of skin, as to be quite purplish owing to the venous congestion. The color varies not only in different persons, but at different periods in the same individual. A bright eruption commonly becomes dusky before it fades.

When the scarlatinal exanthem is viewed at a little distance it gives

the impression of a uniform reddish blush. When, however, the skin is closely scrutinized it is seen that it is made up of innumerable reddish points or puncta. These are of a deeper tint than the skin intervening between them.

At times eruptions are seen in which the skin between the puncta is of normal coloration. This appearance may occasionally be noted during the coming out or evolution of the exanthem. Ordinarily the points of greatest color intensity are surrounded by areolæ of somewhat brighter hue. When these coalesce, as is usually the case, a diffuse eruption is presented, the puncta being scarcely distinguishable through the obliteration of contrast. At times the areolæ are narrower, exhibiting a little intervening normal skin and giving the eruption a more or less *speckled* appearance. In other cases with larger pale areas a *mottled* appearance is noted. Finally, there may exist large, irregular patches of healthy skin, particularly on the arms, legs and buttocks, producing so marked a *blotchiness* of the exanthem as to suggest a strong resemblance to measles.

The scarlatinal eruption frequently exhibits small pin-point to pin-head-sized, reddish elevations, which occur most commonly at the sites of hair follicles. These are frequently seen upon the extremities, particularly the lower, but may also appear upon the trunk. This condition was called by the older writers *scarlatina papulosa*.

In addition to these elevations a general *goose-flesh* condition of the skin is not infrequently observed. This is best marked upon the abdomen and chest, and is characterized by numerous pin-head-sized papules bearing a close resemblance to the "cutis anserina" evoked in the normal skin by exposure to either extreme of temperature. These papules may be faintly red or of the normal skin hue. They differ from ordinary goose-flesh in that they persist usually for some days. At times this condition is so pronounced as to impart to the skin a "nutmeg-grater" feel and appearance.

In the older descriptions of scarlet fever one reads of the occurrence of sudamina at the height of the efflorescence. Inasmuch as during this stage the skin is hot and dry with no tendency to sweating, one would not expect to find sudaminous sweat vesicles. It is extremely common, however, to find in well-developed rashes innumerable *miliary vesicles*. To this condition the term *scarlatina miliaris* or *scarlatina vesicularis* has been given. The vesicles are conical, epidermal elevations, pin-point- to pin-head-sized (size of millet-seed), with turbid or lactescent contents, and usually disseminated, although occasionally occurring in groups. They are commonly situated on the abdomen and chest and to a lesser extent on the extremities. The region in which they are frequently most copiously present is the mons veneris, for here the erythema is often intense. In this region they are prone to develop into minute but well-marked, yellowish pustules.

Rarely, contiguous vesicles may coalesce, forming blebs of the size of a pea or larger, constituting the *scarlatina pemphigoidea* of the older writers.

Miliary vesicles may be seen in nearly all well-pronounced scarlet-fever eruptions. They are much more frequent than is generally supposed, being often overlooked on account of their minute proportions. A magnifying glass will often bring them into view when they are not clearly perceived by the unaided eye. In perhaps 20 per cent of all cases and 50 per cent of well-pronounced eruptions, vesicles are readily visible if looked for; lesions of this size, however, do not intrude themselves upon one's vision upon cursory inspection of the rash. The vesicles are more conspicuous in severe eruptions than in mild rashes.

FIG. 88.—Miliary vesicles with lactescent contents appearing about the axilla with the rash of scarlet fever.

In decidedly exceptional instances they may be so pronounced as to overshadow the general scarlatinal exanthem and puzzle the physician in the diagnosis. Dr. J. P. C. Griffith, of Philadelphia, has reported several such cases.

Gee, Squire, Bohn, Rilliet and Barthez, D'Espine and Picot, Moizard, Baginsky, Vogel and others believe that miliary vesicles are determined by an excessive degree of inflammatory action of the skin. Thomas, on the other hand, thinks that the miliary vesicles are produced by a peculiar disposition of the skin of patients. He states that

in some epidemics this condition has been noticed so often and in such abundance that the normal eruption was observed only in a minority of cases. Griffith[1] fully coincides with the latter view. He cites cases in which extensive miliary eruptions accompanied mild scarlatinal rashes. He feels that it is perfectly possible in occasional cases to have the presence of an abundant miliarial eruption cause decided difficulty in the diagnosis and even lead to error.

In a large experience with scarlet fever we have found miliary vesicles to be much more frequently associated with intense rashes than with mild eruptions, although they may occasionally be seen in the latter.

The older writers seemed to think that this miliary eruption accompanied certain epidemics of scarlatina, and they fancied that these "miliary epidemics" represented a peculiar infection rather different from ordinary scarlet fever.

During the period of the fading and decline of the eruption pea-sized or larger, flat, epidermal elevations are often noted. These are whitish and suggest sudamina, the contents of which have been absorbed, for one seldom, if ever, discovers fluid in them. They may be readily opened with a needle, and resemble empty pea-pods. The exfoliation of the summits of these lesions and of the miliary vesicles constitutes the beginning desquamation on the trunk, but this will be later referred to.

The character of the *eruption on the face* varies somewhat. In some cases this region remains entirely free. More commonly the temples and cheeks are the seat of a deep-red flush; it is probably that this flushing is often associated with the true rash, for it is not rare to see the face desquamate profusely. The forehead often shows redness, but this is usually less intense than on the lateral aspects of the face. The tip and alæ of the nose and the upper and lower lips and the chin commonly appear preternaturally pale. This *circumoral pallor* defined by the marked flushing of the cheeks gives the patient a most curious appearance, which, if not peculiar to, is always strongly suggestive of scarlet fever.

On the *arms and legs* the rash exhibits no peculiarities save its likelihood to early involve the flexures of the joints (groins, popliteal spaces and elbow flexures), and its greater tendency to be *blotchy*. Upon the palms and soles the eruption is usually diffuse red without any puncta.

When pressure is made upon the scarlatinal rash a momentary pallor is produced then a return of redness and finally a gradual paling again which persists for some minutes. We have seen on the legs pale bands persist where garters had previously been worn.

Indeed, one may inscribe a name upon the efflorescence with a blunt instrument and in a few moments note the white letters stand out upon the red background. This is the reverse of the ordinary dermographism and might be termed *anemic dermographism*. This is a vasomotor

[1] Scarlatina Miliaris, Jacobi's Festschrift, 1900, p. 182.

peculiarity, but it is doubtful whether it possesses any reliable diagnostic value.

Itching is not infrequently experienced by scarlet-fever patients. While in most cases it is insignificant or entirely absent, it is occasionally quite severe. It may be noted during the early evolution of the eruption, at its height or during the decline just before desquamation sets in.

In intense eruptions there is often some *edema* and *swelling* of the skin accompanied by an exaggeration of the lines of cleavage. The skin under such circumstances is thickened and shows wrinkling of the epidermis.

On the other hand, the eruption may be so *mild* as to make the diagnosis difficult and even impossible. Indeed, in rare cases the eruption may be absent altogether.

The eruption persists at its maximum intensity but for a brief period —from a few hours to a day or two, and then gradually fades. Much variation is shown as to the entire duration of the exanthem; ordinarily the eruption lasts from *three to seven days*, but its life may be shorter or longer than this period. Cases doubtless occur in which the eruption is of such brief duration as to escape notice entirely; instances of scarlet fever without eruption, but followed by desquamation, are probably to be accounted for by evanescent undiscovered eruptions.

In some cases a temporary *fading or recession* of the rash occurs. It is not rare for the exanthem to be more vivid in color at certain times. The rash is not infrequently brighter in the evening than during the day. It is more rare for the eruption to recede completely and later reappear.

The Enanthem, or Mucous-membrane Eruption.—As has already been stated, sore throat is not infrequently among the earliest of the symptoms ushering in an attack of scarlet fever. In the very beginning there are commonly seen congestion and swelling of the tonsils, uvula and soft palate. A punctated redness is often visible on the soft and hard palate. During the eruptive stage the gums and buccal mucous membrane usually exhibit some redness and swelling.

If the gums are inspected from the second to the fifth day there will oftentimes be seen *milk-white patches* which look much as if they had been produced by the application of pure carbolic acid. These represent a desquamation of the epithelial covering of the gingival mucous membrane, and can readily be peeled off by slight friction. This process occurs at times in measles and perhaps also in other affections in which there is congestion of the oral mucous membrane.

The tongue is, as a rule, heavily covered with a grayish fur at the onset of an attack of scarlatina. Soon the tip and edges assume an angry, reddish coloration and a roughened or granular appearance.

At this time also the fungiform papillæ on the dorsal surface of the tongue become swollen and prominent and peep through the surface coating. Usually by the fourth day or thereabouts lingual desquama-

tion takes place and the coating is cast off, disclosing to view a red, raw-looking, often glazed surface studded with enlarged papillæ.

At times the papillary elevations are numerous and small, looking like the granulations in a wound At other times they are scattered and more prominent. This condition of the tongue is of considerable diagnostic importance and has been variously described as the "raspberry," "strawberry" or "cat's tongue." It should be remembered, however, that mild cases of scarlatina occasionally exhibit no abnormality of the tongue whatsoever.

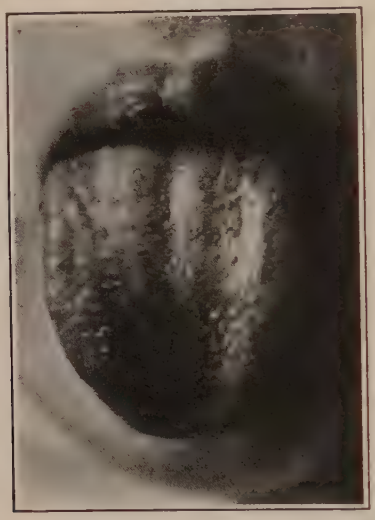


Fig. 89.—So-called "strawberry tongue," showing the enlargement of the lingual papillæ.

During the eruptive stage the condition of the throat undergoes aggravation. The tonsils are usually enlarged, reddened and covered with a layer of muco-pus or actual pseudomembrane. The uvula, anterior pillars and soft palate are intensely reddened and edematous. The patient complains of much pain in the throat, particularly on swallowing.

Desquamation.—Exfoliation of horny epithelium begins during the decline of the eruptive stage. Desquamation occurs first upon those parts of the cutaneous surface which were first the seat of the exanthem (Fig. 90). Where the face has presented much eruption, or even intense flushing, a branny desquamation will often be noted as early as the fourth day. Almost simultaneously a similar epidermal exfoliation occurs upon the neck and the upper portion of the chest. This process is commonly inaugurated about the sixth or seventh day of the disease.

If one watches for the first evidence of desquamation on the trunk

PLATE XVI

Desquamation upon Face, Neck and Chest.

Sixth day of the disease.

it will be noticed as a number of discrete pin-point-sized, powdery scales. These represent the desiccated summits of the miliary vesicles. In a day or two these small scales are cast off, leaving minute, jagged rings of desquamation. The horny layer is now lifted off by centrifugal extension of these rings, which grow progressively larger. On meeting enlarging rings of neighboring lesions they produce gyrate and geographic configurations resembling the contours of maps. In this manner the upper layer of the corneous stratum is removed. In some cases about the sixth or seventh day there develop on the trunk, as discussed more fully later (page 429), epidermal elevations which apparently contain air, and from which extensive desquamation starts. It would appear that the scaling on the trunk has its origin almost invariably in the miliary vesicles and in the air vesicles.

FIG. 90.—Desquamation upon the face; fifth day of scarlet fever.

Upon the hands and feet the desquamation is of quite a different character. Here the horny layer is shed either in large flakes or more rarely *en masse*, with the result that a partial or complete epidermal cast is thrown off, resembling a glove or a slipper.

It is seldom that these epidermal gloves remain intact until complete exfoliation, unless the hands are kept bandaged.

The most typical and characteristic scarlatinal peeling, however, is that which begins about the free border of the nail. Just beneath the edge of the nail a fissuring or cleavage of the horny layer takes place, the latter being stripped back toward the finger-tip, and thence up the finger. The peeled portion of the finger exhibits to view the new, soft, pinkish skin, whereas beyond is seen the harsh, horny cuticle. This desquamation originating in *subungual cleavage* of the epidermis is of considerable diagnostic import; it is seen also upon the toes, but not so well pronounced.

Before desquamation begins upon the hands the skin becomes harsh, dry and wrinkled. The occurrence of peeling may by attention to this condition be determined in advance.

In some cases, particularly when the rash is extremely mild, desquamation may be so slight as to be scarcely perceptible. Indeed, in rare cases it may be entirely lacking.

FIG. 91.—Unusually severe desquamation in a case of scarlet fever with an intense eruption. Enlarging scaling rings are well shown.

On the other hand, it may be so intense as to resemble the affection known as exfoliative dermatitis. This is the form which is apt to be attended with exfoliation of large strips of epidermis and casts of the hands and feet. Other epidermal structures, such as the hair and nails occasionally become affected, in which event the hair and nails are shed. Where the nails are not actually thrown off they may show a transverse furrow which in the course of time grows out to the free edge.

Duration of Desquamation.—The duration of desquamation cannot be stated in definite terms, as it is subject to the greatest variation.

There are mild cases in which no desquamation can be detected after two weeks. On the other hand, severe cases, and even some mild cases, may continue to desquamate for eight, nine or ten weeks. Indeed, where the rash has been intense a second and even third scaling may occur after the first desquamation has been completed.

Secondary desquamations are not particularly uncommon, although

PLATE XVII

Extensive Desquamation following a Severe Rash.

Ninth day of disease.

it is rare to observe the exfoliative process repeated more than a second time. When scaling occurs more than once the subsequent desquamations are, as a rule, not general, but limited to certain areas, particularly the palmar and plantar regions. The scales usually come away in the form of small or large flakes.

Thomas refers to a case of Jadious in which the scaling repeated itself five or six times. These repeated epidermal exfoliations protract the period of desquamation almost indefinitely. Scaling persists longest on the hands and feet, particularly the latter. Our experience would lead us to say that the average duration of desquamation in well-marked cases of scarlatina is about six weeks.

FIG. 92.—Well-marked desquamation upon the dorsum of the hands and fingers.

The degree of intensity of desquamation is, as a rule, proportionate to the intensity of the eruption, but there are numerous exceptions to this rule. Many writers state that true scaling may occur upon parts of the body which have not been the seat of any exanthem. We prefer to believe that in these cases there has been a fugacious but unobserved eruption present. It is quite possible for a rash to be present during the hours of the night and, disappearing in the morning, completely escape observation. We cannot conceive of characteristic desquamation occurring without some previous vascular disturbance in the skin.

We recall the case of a ward maid who, after a few days' exposure to scarlatina, contracted a severe sore throat with fever, and who scaled profusely on the hands and feet, although no true eruption had ever

been discovered. It is, perhaps, nearer to truth to say that a rash was not seen rather than that it was not present.

If the skin is closely inspected distended cutaneous capillaries will often be found to be visible to the naked eye. It is not uncommon in intense rashes to note the presence of scanty, claret-colored, *petechial* extravasations into the skin. These are noted particularly in regions where the skin is thin and tender, such as on the neck, axillary folds, inner sides of the arms, flexures of joints, etc. These hemorrhages betoken intensity of the eruption rather than malignity of the infection. To be sure, in malignant cases the eruption may be hemorrhagic, but under such circumstances the extravasations into the skin are larger and accompanied by bleeding from some of the mucous membranes.

FIG. 93.—Epidermal glove-like casts from a fatal case of scarlet fever.

Lymphatic Glands.—Intumescence of the lymph glands may be regarded as an almost constant accompaniment of scarlet fever. It would appear that the scarlatinal poison is responsible for the changes in a lymphatic structures, for not only are the subcutaneous lymph glands affected, but also the lymphoid elements of the liver, spleen, intestines, etc. On this account Hawley has suggested that the term lymphatic fever be substituted for scarlet fever.

Quite early in the course of scarlet fever do we note an appreciable

tumefaction of the subcutaneous lymph glands, more particularly those situated about the angles of the jaws.

The following presentation of the condition of the glands in 100 cases[1] will give an adequate idea of the extent of the lymphatic involvement in scarlet fever.

FIG. 94.—Pronounced desquamation in large lamellæ.

The various lymphatic glands were enlarged in the following proportion of cases:

		Per cent.
Inguinal glands		100
(*a*) Pea-sized	23	
(*b*) Bean-sized	77	
Axillary		96
Maxillary		95
Posterior cervical		77
Anterior cervical		44
Submaxillary		36
Epitrochlear		26
Sublingual		25

The inguinal glands were in the main enlarged to the size of a pea or bean, although occasionally they would reach the dimensions of an almond.

The epitrochlear glands vary from the size of a lentil to a pea. Not infrequently the enlargement occurred but upon one side. Occasionally there is a second enlarged gland just above the epitrochlear gland.

The axillary glands vary in size from a pea to an almond. They are usually enlarged in clusters rather than singly.

[1] Schamberg, J. F.: A Clinical Study of the Lymphatic Glands in One Hundred Cases of Scarlet Fever, Ann. Gynec. and Pediat., December, 1899.

The sublingual gland is scarcely ever larger than a lentil seed. The submaxillary lymphatic glands were found to vary in size from a pea to an almond. In one case a gland reached the dimensions of an orange, broken down and suppurated.

The maxillary glands, or those just behind the angle of the jaw, reach the largest size of any of the lymphatic glands and are the commonest to undergo suppuration. In the above cases they varied from the size of a bean to that of an orange. The average was perhaps represented by the dimensions of an almond or hickory nut.

The anterior cervical glands, or those lying in front of the sterno-cleido-mastoid muscle, were usually pea- to bean-sized, as were also those posterior to the muscle.

The glands were examined at various stages of the disease, as early as the second day and as late as the fifteenth. In the cases studied upon the second and third days the glandular enlargement was so well marked as to suggest the probability that the glands are already somewhat tumefied on the first day of the illness.

The duration of the enlargement doubtless varies in different patients. In several cases, examined at intervals of a few days for three weeks, the glands were found to gradually diminish in size, but at the end of this time they were still slightly enlarged.

Statistics are frequently misleading, and those presented above are, perhaps, no exception to the rule. While it is true that the inguinal glands were enlarged in every one of the 100 cases of scarlet fever examined, it is more than probable that in some of them the enlargement antedated the attack of scarlet fever. The percentage of apparently healthy children with pea-sized or larger inguinal glands must be very considerable. Still the effort was made to eliminate this error as far as possible. It is in most cases not difficult to distinguish between an old and a recently enlarged gland. The former has a decidedly sclerotic feel, with the resistance, say, of cartilage. The latter presents a peculiar resiliency with the consistency of liver.

The enlargement of the glands about the jaw and neck is ordinarily proportionate to the amount and intensity of throat involvement. There are, however, occasional exceptions to this rule, and it should be recognized that extensive lymphatic swelling may occur with but slight throat symptoms.

When the glandular swelling is of moderate extent and of early occurrence it usually undergoes gradual subsidence. When the swelling is very great, and particularly when it develops late, from the second to the fourth week of the disease, it is extremely prone to suppurate and form a glandular abscess. This will be further referred to under the subject of complications.

Respiratory Symptoms.—**Laryngitis.**—Despite the intense inflammation of the pharynx in scarlatina there is but little tendency to involvement of the laryngeal structures. Trousseau's epigrammatic saying, "Scarlatina has no liking for the larynx," is borne out by experience.

He further remarks: "True scarlatinous sore throat, then, is pharyngeal, differing in this respect from the sore throat of measles, which is laryngeal, and from that of smallpox, which is both pharyngeal and laryngeal."

It is only when the inflammation of the throat in scarlatina is severe, with tendency to gangrenous change, and is accompanied by swelling of the surrounding connective tissue, that the larynx may become compromised. In such cases both the mucous membrane and the connective tissue of the larynx may undergo inflammation.

True, the larynx may become involved later in the course of the disease by the formation of ulcerations or the development of a pseudo-membrane, which may or may not be due to the diphtheria bacillus.

Bronchial Catarrh.—In severe cases of scarlet fever a catarrhal condition of the bronchial tubes may be present even in the early stages of the disease. In malignant cases that have proven fatal after an illness only of a few days, it has not been uncommon on autopsy to find an inflamed condition of the bronchial mucous membrane, with the presence of a muco-purulent exudate. Henoch,[1] Jürgensen and others have recorded such cases. The former says: "The mucous membrane of the bronchi and the parenchyma of the lungs are excited by inflammatory influences far more frequently than we usually suppose. Not only catarrh, but more or less extensive bronchopneumonia, occurs in the first and second weeks of the disease. These conditions are frequently overlooked, however, because a whole series of synchronous, severe typhoid symptoms disguise them and divert the attention of the physician. We found bronchitis and bronchopneumonia in nearly all the severe cases, and also repeatedly during life."

Pneumonia.—Pneumonia either of the catarrhal or croupous variety is an uncommon occurrence in scarlatina; when it does occur it is usually in connection with severe cases of the disease.

Leichtenstern is authority for the statement that "in children acute lobar pneumonia, sometimes bilateral and mostly involving the upper lobes, appears as well in the height of the disease as in the nephritic stage. These are pneumonias such as in the shortest space of time lead to a complete infiltration of a whole upper lobe, or more rarely a lower lobe."

Gastro-intestinal Symptoms.—Vomiting occurs at the beginning of the disease in a large percentage of cases of scarlatina. In some severe cases the vomiting may continue for some days or may return after it has ceased. This may be accompanied by pains in the epigastrium. The *bowels* at the onset of scarlatina may be normal or constipated. In some cases, however, diarrhea is present and in some instances it may be quite severe. In bad cases a persistent diarrhea with greenish or bloody stools is often observed. This serves to increase the already existing weakness and prostration, and therefore adds to the gravity of the disease.

[1] Vorlesungen über Kinderkrankheiten, 3d ed., p. 642.

The *nasal mucous membrane* usually remains normal in scarlet fever. When the nose is involved it is usually the result of extension of a secondary infection from the throat. In scarlet fever of the anginose form the mucous membrane of the nose may become reddened, swollen and secrete a foul, muco-purulent or bloody discharge, which excoriates the nostrils and adjacent portions of the skin. Ulceration of the mucous membrane may occur, occasioning the loss of considerable tissue.

Severe involvement of the nose is rare in simple scarlatina; it is much more common in the anginose variety.

Roger[1] mentions a severe purulent rhinitis which develops early in some cases of scarlet fever. The profuse discharge from the nose is accompanied by tremendous swelling of the cervical glands and suppurative otitis. Occasionally extension of inflammation to the antrum or the frontal sinus occurs, as in a fatal case quoted by Roger. The streptococcus is looked upon as the cause of the purulent inflammation. We have not infrequently observed purulent rhinitis in anginose scarlet fever.

The *mucous membrane of the lips* is commonly swollen and reddened. The epithelial covering is often lost, leading to superficial ulcerations which are prone to bleed and become covered with crusts. The commissures of the mouth may be fissured, the rhagades extending into the true skin and causing considerable pain.

Scarlatina Anginosa—Severe or Septic Scarlet Fever.

This form of the disease is characterized by an excessive development of all of the symptoms, but with particular severity of the throat manifestations. The aggravated nature of the attack is usually manifest from the outset. The incubative and invasive periods are usually short; with headache, chilliness and vomiting, the temperature rises suddenly to 104° or 105° F.; with the appearance of the eruption, which develops commonly within a few hours of the initial symptoms, the pyrexia may still increase until a burning fever of 106° or 107° F. is reached. The temperature in this form is not only higher than in simple scarlatina, but it is also of longer duration. The temperature during the first five or six days commonly fluctuates between 104° and 105° F., and then in cases that end in recovery declines by slow gradation in the course of two, three or four weeks to the normal line.

The nervous symptoms are pronounced; delirium is commonly present, alternating with periods of somnolence or semi-coma. At times jactitation with extreme restlessness and wakefulness are noted. With children there is persistent disposition to sleep, great irritability when awakened and stubborn resistance against taking nourishment. There is not only complete anorexia, but also painful deglutition which prompts the patient to reject the proffered food.

[1] Les maladies infectieuses, p. 346.

The rash is usually intense, covering the entire body, not excluding the face. Indeed, in bad cases the face often shows an intense deep-red, sharply marginated, eruptive flush on the cheeks, which persists for some days. The eruption is of vivid hue, at times acquiring even an erysipelatous appearance. In other cases the distribution may be irregular, the eruption occurring *in patches* upon the hands and feet, flexures of joints, buttocks, legs, etc.

In a fatal case in a child, aged eight months, under our care there were fiery-red patches on both cheeks, an intense erysipelatoid rash on the legs, and a faint punctate eruption on the trunk.

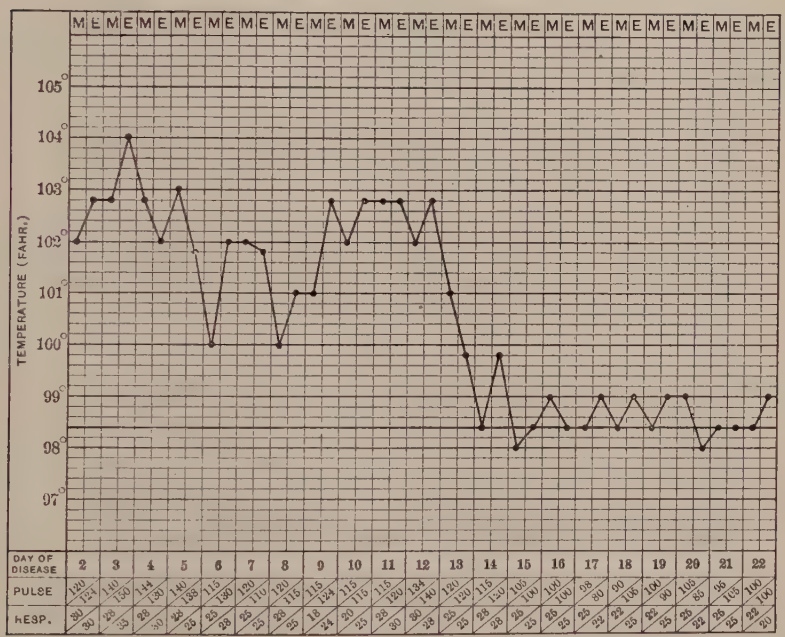


FIG. 95.—C. S., aged twenty-five years. Woman with the anginose form of scarlet fever, treated at the Philadelphia Hospital for Contagious Diseases. Subsidence of temperature on the fifteenth day. Recovery.

The pulse is rapid, frequently running between 120 and 150 per minute; it is likewise weak and compressible and often arrhythmical.

The glands at the angles of the jaw become rapidly swollen; they commonly attain the size of a walnut or even a small apple. The surrounding cellular tissue participates in the general inflammatory process, producing great cervical intumescence and often causing the child's head to be bent backward.

Upon inspection of the *throat* the tonsils, arches, uvula and soft palate are, during the first couple of days, seen to be intensely reddened and edematous. Even at an early date there is a hypersecretion of a viscid, stringy mucus, which adheres to the tonsils and soft palate,

and, becoming dry as a result of the mouth breathing, occasions much annoyance to the patient. Commonly by the third or fourth day a membranous exudate appears upon the tonsils, uvula and soft palate, extending often to the pharynx and posterior nares. The occlusion of the nasal channels further obstructs the ingress of air and distresses the already harassed patient. The buccal and alveolar mucous membrane is greatly congested and often the seat of ulcerations from which blood oozes. The teeth, gums and lips are covered with sordes, and an offensive, at times fetid, odor is emitted from the mouth. The tongue is of an angry-red color and occasionally ulcerations, covered with a grayish exudate, are seen upon the edges. As has been stated, the nose discharges a purulent material and commonly shows ulcerations of the mucous lining. The eyelids may also become inflamed, the conjunctiva congested and a purulent discharge issues from the palpebral cleft.

The child is often unable to swallow, water or milk being ejected through the nose. The nasal and faucial respirations are of a rattling character and painful to behold.

The extension of the morbid process along the Eustachian tubes leads to a purulent inflammation of the middle ear on one or both sides. Rupture of the tympanic membrane occurs with the evacuation of the purulent accumulation. The external auditory canals become infected by this discharge, and often develop ulcerations which may eat quite deeply into the tissues.

The child with a bad anginose scarlatina is a pitiable object—it lies with the head back to prevent the pressure of the swollen glands from compromising the breathing; the neck is greatly tumefied, the overlying skin stretched and glazed, the commissures of the mouth fissured and covered with blood crusts, the nose discharging a sanguino-purulent matter, the eyelids swollen and the ears expelling a thin, ichorous pus. Indeed, every orifice of the face gives issue to a putrid and foul-smelling discharge, which contaminates the atmosphere about the patient with the stench. The general symptoms are those of a profound septicemia.

In extremely bad cases, and in our experiences more particularly in mixed cases of scarlet fever and diphtheria, extensive ulceration and sloughing of the tonsils or soft palate may take place. The *necrosis* in such instances involves the entire thickness of the tissues, and leads commonly to perforation of the soft palate. We have in a number of cases seen these *perforating ulcers* of the soft palate; they may be bilateral, or occur only upon the one side. The accompanying symptoms are of a septic character, and the prognosis is unqualifiedly bad; death takes place in almost every case.

In fatal cases of anginose scarlatina death may occur as a result of the severe primary blood poisoning, or through the development of the latter complications, such as nephritis, pneumonia, endocarditis, etc.

Bronchopneumonia is more frequent than is commonly believed,

the symptoms being masked by the severe angina and the grave toxemia.

The urine is diminished in quantity and nearly always contains albumin. The microscope will often discover the presence of tube casts and also red blood corpuscles.

A fatal termination is preceded by rise in the temperature to 106° or 107° F., an increasing prostration and stupor, and a progressive weakening and augmented frequency of the pulse. Fatal cases usually succumb during the first or second week of the illness.

In severe cases of anginose scarlatina the lymphatic glands and adjacent tissues, under the influence of intense inflammation or, perhaps, a special infection, may undergo *gangrene*, leading to great sloughing and even alarming or fatal hemorrhage from the erosion of some large bloodvessel. Trousseau speaks of a case in a boy, aged fourteen years, "in whom the gangrene condition was so extensive that the muscles of the neck were dissected, as occurs in diffuse phlegmonous inflammations, showing the carotids pulsating at the bottom of a horrible wound."

In cases that end in recovery the temperature at about the end of a week or ten days begins to decline, the pulse slows and acquires better volume, the marked nervous symptoms gradually disappear, and the throat and adjacent cavities show a lessening in the intensity of the inflammatory process. The decline in the temperature is slower and less regular than in the usual type of the disease, and the normal is seldom reached before the end of the third or fourth week. Convalescence is apt to be complicated by nephritis and in some cases by rheumatism and endocarditis.

Scarlatina Maligna.

Malignant scarlatina, a fortunately rare form nowadays, is characterized by such a sudden overwhelming of the vital forces as to cause death in a few days, or, indeed, within twenty-four hours. The symptoms, consisting of extremely high fever, severe brain symptoms and profound prostration, with or without hemorrhages into the skin and from the mucous membranes, develop with fearful rapidity, and the patient sinks under the dread influence of the poison.

The abruptness of the onset of the disease in these cases is remarkable. Children in the enjoyment of apparent perfect health may be smitten while at play. The child has a severe attack of vomiting, which may be accompanied by purging, and is followed by convulsions or stupor. The temperature rises rapidly to 107° or 108° F., the pulse to 140 or 150. Great restlessness and delirium may alternate with stupor. Excruciating headache and violent pains in the extremities are sometimes present.

The eruption is usually irregular, appearing often on the hands and feet before it is seen on the body. At times it appears only about the

flexures of the joints. The rash may recede after a brief presence, only to appear a few days later. It is sometimes partial, assuming an erysipelatous aspect on the face or legs. It has commonly a livid hue, being beset with petechiæ and vibices.

The local symptoms in malignant scarlatina are severe. The throat is so intensely swollen that swallowing is often impossible. The glands are greatly enlarged, and, if the patient lives long enough, the nose and middle ear become involved.

Prostration and collapse may occur so suddenly that *no eruption* appears. The skin is pale or livid, the lips blanched, the eyes glassy and sunken with partial closure of the lids, the surface cold, the pulse weak and fluttering and death imminent and inevitable. This choleraic type at times cannot be diagnosed without the presence of other cases of scarlet fever in the same household.

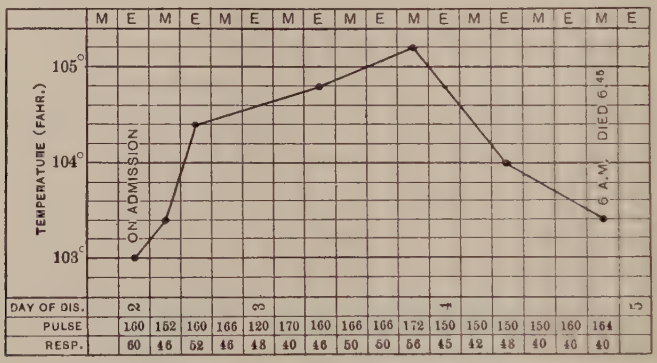


FIG. 96.—W. R., aged three years. Case of malignant scarlet fever with high temperature dying upon the fifth day of the disease.

These rapidly fatal cases are rare, but well-authenticated instances are recorded. Morris[1] speaks of a child that was taken out apparently in perfect health for its morning airing and brought back within an hour with stupor and general muscular relaxation, cold surface, feeble pulse and total insensibility; death occurred in twelve hours. Within a few days 2 other children in the same family were seized with scarlet fever which ran a regular course. Dr. Rush reported "a few instances of adults, who walked about, and even transacted business, until a few hours before they died." Such a case is mentioned by Morris: "A judge of one of the courts was seized with nausea while on the bench and retired to his home, where for two days he remained, scarcely willing to admit himself to be sick, and reluctant to confine himself to his chamber, though the rapid, feeble pulse and an imperfect eruption too plainly indicated the nature of the affection; on the third day he died while in the act of shaving himself." A near relative stood beside the corpse and contracted a similar fatal illness.

[1] Pathology and Therapeutics of Scarlet Fever, Philadelphia, 1858.

Gregory,[1] in referring to malignant cases, says: "In some extreme cases . . . all the ordinary appearances of scarlet fever are masked; petechiæ, coma and a sloughy state of the throat alone appear." And further he remarks there are cases "where no affection of the skin takes place at all." As an instance thereof, he attended a woman and two grown-up daughters, in all of whom "the nervous system was utterly prostrated, or in the state of collapse. There was no violence, no delirium, no struggling for breath, no rash; but the pulse was small, the skin cold and the whole system depressed by the intensity of the poison. . . . They sank one after the other, without any attempt to rally. It was difficult to believe the disease scarlatina, but the eldest son took it in the usual form, recovered and put the matter beyond doubt."

Hemorrhagic Scarlatina.—Another form of malignant scarlet fever remains to be described, namely, hemorrhagic scarlatina. This type of the disease is ushered in by high fever, severe prostration and marked brain symptoms. A dusky-red erythema, usually imperfectly developed, is seen upon the skin and is soon followed by the appearance of scattered wine-colored or purplish, pin-head and larger sized petechiæ, and later ecchymoses. As in hemorrhagic smallpox, bleeding occurs also from the various mucous membranes, the nose, mouth, intestines, kidneys, etc. Epistaxis and intestinal hemorrhages are the most frequent and serve to exhaust the vitality of the patient. Vomited matter may show the presence of blood and thus early indicate the malignant character of the attack. The presence of blood in the urine may result from renal hemorrhage or oozing lower down in the urinary system. Women may bleed profusely from the uterus. If the patient escapes the blighting influence of the high fever and intense toxemia he is pretty sure to be prostrated by the hemorrhages from the mucous membranes, or leakage into the brain or the other viscera.

The condition of the throat and lymphatic glands is, in bad cases, similar to what is encountered in the anginose form. These cases are almost invariably fatal; the pulse becomes feeble and rapid, the respirations quick and shallow and the patient lapses into a terminal coma.

The occasional reddish hemorrhages into the skin which accompany intense eruptions in well-marked attacks of normal scarlet fever and which are particularly seen upon dependent portions of the body, such as the back, should not be confounded with the malignant hemorrhagic form just described.

Thomas[2] calls attention to an irregular form of scarlet fever in which, with very moderate or trifling local symptoms, there occurs a severe protracted fever. This has been designated *typhoid scarlatina*, although no real connection with true typhoid fever is suggested. The protraction of the fever for three, four or more weeks may be wholly, partially, or not at all attributable to local complications. At the outset there

[1] Loc. cit.

[2] Loc. cit.

are marked cerebral symptoms, severe headache, delirium, somnolence and great thirst. The eruption comes out promptly, but is often poorly developed, the same being true of the throat symptoms. Desquamation occurs, but the skin remains hot and feverish. Later the patient becomes apathetic and very deaf without accountable ear trouble; there is enlargement of the spleen, pulmonary congestion and diarrhea. Apart from the glandular enlargement, there are no local complications, and one is at a loss to explain the remittent fever, which now continues for weeks. Nephritis may develop and cause a continued high fever, which may sink to normal with the subsidence of the renal complication. Typhoid cases of this character that come to autopsy usually show, besides the usual scarlatinal changes, congestion of the meninges and brain, catarrhal inflammation of the respiratory organs, hypostasis of the lungs, effusions into the serous cavities, splenic and hepatic enlargement, swelling of the mesenteric glands, prominence of the follicles of the small intestines, and even some tumefaction of Peyer's patches. In some of these cases, according to Thomas, a peculiar secondary scarlatinal eruption develops which differs from the first in that it is not a diffuse erythema, but of the nature of a *roseola*. The lesions are generally of a dark, rather scarlet-red color, at the same time smaller and less sharply defined, generally closer together, and less elevated above the surrounding pale skin than is the case in measles. The eruption may occur only on the face and extremities, or may be copiously distributed over the body to an extent even as to render the macules confluent. The rash may disappear in twenty-four hours, or may remain several days. It is followed by an intense lamellar desquamation. There is a concomitant congestion of the throat, some renewed tumefaction of the glands and the lingual papillæ again become enlarged. Thomas considers this eruption as an irregular form of scarlet fever, and looks upon its development in the light of a pseudo-relapse. This curious complication is not of grave import, as most of the patients recover.

Irregular or Aberrant Scarlatina.

The symptoms described under the title of scarlatina simplex may be considered as representing the usual or normal manifestations of scarlet fever. The anginose and malignant varieties are, in a sense, deviations from the classical form, and, therefore, irregular. In addition there occur from time to time, in connection with the more important symptoms, phenomena which have given rise to the term *irregular scarlatina*.

Irregularities of the Fever. – Cases of scarlatina accompanied by extremely high temperatures, reaching 107°, 108°, 110° F. have already been referred to. Such hyperpyrexia usually indicates malignancy and a fatal termination. The *protraction of the fever* for weeks has also been mentioned in connection with the so-called typhoid scarlatina.

Scarlatina may, in rare cases, occur *without fever* (*scarlatina sine febre*). It is not uncommon to encounter very mild cases in which the temperature, after a brief and moderate rise for a day or two, sinks to the normal and remains so. Such cases may present all of the usual symptoms, but in a very moderate form.

In a series of cases reported by McCollom, 37 had temperature not exceeding 99° F. It has been doubted that true scarlatina occurs without any rise of temperature whatsoever. Wunderlich[1] expresses this doubt in the following terms: "Whether among these abnormally mild cases there also occur those in which the temperature shows absolutely no change . . . I cannot say from my own experience, because I have never been able in very light cases to observe the beginning of the disease." Von Jürgensen mentions 2 cases in his practice in which there was practically no fever. In 1, a child, aged three and a half years, with a well-marked scarlatina, the temperature was below 98° F. during the entire illness, with the exception of one or two occasions, when it momentarily rose to about 100° F. In a second case also the temperature never rose above 100° F.

We had under our care a child with scarlatina which developed in the hospital and in which we were enabled to watch the temperature record for four days preceding the attack. M. S., aged nine years, was admitted to the scarlet-fever ward of the Philadelphia Hospital for Contagious Diseases from a foster home in which there was an epidemic of scarlatina. The patient had on admission (January 10, 1903) such indefinite symptoms as to scarcely permit the diagnosis of scarlet fever. On January 14th, four days after admission, she vomited and a well-marked scarlatinal rash appeared over the entire body. At this time her temperature registered 99° F.; on January 15th and 16th it declined to normal and then to 98° F., rising to 100° F., on January 17th and then again falling to normal.

Irregularities of the Eruption.—The scarlatinal eruption may depart from its usual appearance and present atypical features. An excessive development of the miliary vesicles to such an extent as to mask the character of the eruption has already been referred to.

Partial Eruptions.—In some very mild cases the exanthem may be *poorly developed and limited* to certain regions of the body. The associated fever and angina are often correspondingly slight. Gregory saw cases in which the exanthem appeared only on the thighs. Thomas speaks of cases in which it is limited to one side of the body, or the upper or lower half of the body, or the lower extremities. Glaser describes a form in which the exanthem appears as a broad band around the neck or around the joints. Wildberg also noted it in the latter situation. Zehnder[2] observed it in the form of red spots scattered over the body.

In exceptional instances the face may remain entirely free of erup-

[1] Das Verhältniss der Eigenwärme in Krankheiten, Leipzig, 1870, p. 330.

[2] Quoted by Thomas: Loc. cit.

tion. This is more apt to occur in mild cases in which the eruption is of only moderate intensity.

The scarlatinal exanthem is sometimes of an intense hue and accompanied by considerable swelling of the skin and even subcutaneous tissue, imparting to the condition an almost erysipelatous appearance.

Poorly developed eruptions are not always indicative of benign attacks, for the exanthem is sometimes *partial* in severe and even malignant cases of scarlatina. Morris[1] says: "It is by no means unusual to meet with cases where all the constitutional symptoms are well marked, though the eruption is confined to the wrists or flexures of the joints, and is there limited to a small number of *red points* only. I have met with many such in families where other cases were well marked. They are frequently fatal."

Malignant cases are often characterized by irregularities in the time of appearance, duration and character of the eruption. The latter is often blotchy, like the eruption of measles; in other cases it is purplish and at times hemorrhagic.

Scarlatina Sine Eruptione, or Scarlatina Sine Exanthemate.—The eruption of scarlet fever is its most conspicuous manifestations, and is commonly the symptom which leads to the diagnosis of the disease. There is general accord among writers on this subject that scarlet fever may in rare cases occur *without an eruption*. In malignant scarlatina death sometimes occurs so quickly that there is scarcely time for the exanthem to appear. The diagnosis in such instances must be confirmed by etiological evidence.

Apart from these cases the estimation of the frequency of *scarlatina sine exanthemate* depends much upon one's comprehension as to what constitutes scarlatina.

Nurses and physicians who are in attendance upon scarlet-fever patients and the adult members of a household in which the disease exists commonly contract a sore throat and fever. This condition has been termed *angina scarlatinosa*, or *scarlatina faucium;* it presents usually the same symptoms as are observed in follicular tonsillitis. These sore throats occur both in individuals who have never had scarlatina and in those who have at some time experienced the disease.

To assume that all of these cases represent instances of scarlatina without eruption would, we feel sure, be unwarranted; to assume that they are all non-scarlatinous would be, perhaps, an equal deviation from the truth. In the present state of our knowledge it is unwise to express one's self with any degree of dogmatism upon this question.

Bohn conservatively expresses himself as follows: "In the vicinity of a scarlet-fever patient febrile indisposition, angina and catarrh of the mucous membranes, vomiting, even diphtheria of the tonsils, in the other members that have already had the disease are almost daily occurrences. We must only accept a case as one of scarlatina, if, dur-

[1] Loc. cit.

ing an epidemic, especially in families where either early or late a distinct scarlatinal case appears, cases occur in which nothing more is lacking from the fully developed picture than the confidently awaited exanthem."

Mayr[1] states that the expression "scarlatina without eruption" is only justified in those cases in which the exanthem is absent, but in which we have otherwise typical attacks with fever, angina and desquamation and, in addition, etiological evidence.

Thomas[2] says: "A slight or moderately severe fever of short duration, accompanied by some pain in the neck and enlargement of the cervical glands, is not an uncommon occurrence in persons who have but little predisposition to the disease, especially if they be of mature years, and also in those who have already had scarlet fever in childhood. These symptoms are the more suspicious if scarlet fever has occurred in the family, or if the patient has probably been exposed to the poison. If the throat be examined the characteristic redness is seen in a mild form, with or without a moderate enlargement of the tonsils; perhaps also the tongue presents the appearance of the scarlet-fever tongue. There are also malaise, anorexia, headache and other symptoms of slight importance. Such attacks generally disappear in a few days, but they should receive the same attention which is paid to the unmistakable disease. *Every throat affection during a scarlet-epidemic is suspicious.*"

That some of these sore throats are cases of true scarlatina faucium is evidenced by the fact that genuine scarlet fever is occasionally contracted from persons suffering from this variety of the disease. Morris[3] records such a case: "The wife of a medical friend of mine, who was aiding in the care of the children of a relative, was seized with this modified affection and communicated scarlet fever in all its integrity to her own children."

Graves[4] refers to a boy who was taken home from a school where scarlet fever was prevailing; he complained of pain on swallowing, slight headache and nausea. The next day the tonsils were swollen and there was increased pain on swallowing; the pulse was sharp, the skin hot, but there was no trace of eruption. These symptoms continued three days and then disappeared. Before the boy had completely recovered his father and two sisters took scarlatina.

Trousseau, Graves and others have reported cases occurring in scarlatina households in which *anasarca* without previous eruption has been the symptom to attract attention to the patient. Trousseau remarks: "I came to the conclusion that the persons who had only had eruption and consecutive anasarca, those who had only had anasarca and those who had only had sore throat had all had scarlatina, the affections seen in all of them being manifestations of that disease."

[1] Scarlatina, Hebra's Diseases of the Skin, English translation, London, 1866.
[2] Loc. cit., p. 251.
[3] Loc. cit., p. 35.
[4] Quoted by Trousseau.

Thomas refers to cases in which the scarlatinal nature of the disease is proved by the subsequent occurrence of the characteristic desquamation, even when there has been no previous trace of an eruption. We have already spoken of a case of a ward maid, in attendance upon scarlet-fever patients, who developed sore throat, enlarged glands and well-marked desquamation without having had a discoverable rash. There was, on close inspection on one day, a faint flush over the chest, but no more redness than is seen at times in health. We believe that all patients who desquamate characteristically have had an exanthem. Desquamation is the terminal stage of certain vascular changes in the skin, and it is inconceivable that a patient should present well-marked scaling without an antecedent eruption. To be sure, the eruption may be of extremely brief duration and may entirely escape observation.

Secondary Septic Erythema.—Occasionally in severe cases of scarlatina of the anginose variety, a dusky red, maculo-papular erythema is observed to occur in the second or third week of the disease. The eruption is most commonly seen about the extensor surfaces of the knees and elbows, although it is at times more extensive and may involve the face and a considerable portion of the surface of the trunk and extremities. This erythema usually persists for two or three days. It occurs in bad septic cases with purulent rhinitis, sloughing throat and discharging ears and is of evil prognostic import. The discharging nose and blotchy eruption may excite suspicion of a superadded measles infection.

Reference has already been made to an extensive, secondary, dark-red roseolous eruption, mentioned by Thomas and regarded by him as a pseudo-relapse rather than an accidental complication.

Scarlatina Without Angina.—In many mild cases of scarlet fever the congestion of the throat is so slight that under other conditions the throat might not be regarded as deviating from the normal. Writers generally agree that in rare cases scarlatina may exist without any angina whatsoever. In those cases in which the sore throat is absent the eruption is usually poorly developed, the fever is very moderate and the entire attack mild.

Bergé[1] reports a series of cases of puerperal and surgical scarlet fever in which there was *not the slightest involvement of the throat*. He believes that the angina in scarlatina represents the site of inoculation of the poison, and cites the above cases to show that infection may take place through other mucous membranes or wounds, in which event the angina may be absent.

Scarlatina Without Desquamation.—As a rule, the extent of the desquamation is proportionate to the intensity of the eruption which precedes it. There are, however, occasional exceptions to this generalization. Severe desquamation may now and then follow mild eruptions, and but slight scaling may develop after a well-marked exanthem.

[1] Pathogenie de la scarlatine, Paris, 1895.

When there has been no discoverable eruption there may be no desquamation, and even at times when there has been but a slight eruption present, the desquamation may be so insignificant as scarcely to be detectable.

Second Attacks of Scarlatina.—In the vast majority of individuals *one attack* of scarlet fever *will protect* against the disease *for life*. While there are many cases on record of second and a few of third and fourth attacks, it is quite obvious that in a disease which so often presents difficulties of diagnosis, the estimate of the number of cases reported must, to a certain extent, be discounted to allow for error. Willan never encountered an instance of second attack among 2000 cases of the disease that he attended. On the other hand, Trojanowsky estimated that 6 per cent of his cases consisted of second attacks. Thomas, in an experience of many hundreds of cases, was able to convince himself of a second attack in only a single instance. Henoch, likewise, noted but a single instance of second attack. Kinnicutt saw two attacks within eight months in a boy five years of age.

Third attacks are of excessive rarity. Sir Gilbert Blane observed three attacks in a young lady "without the least suspicion of ambiguity or possibility of mistake in diagnosis." Richardson, Gillespie, Murchinson, Bins, Moore and Thompson have also recorded third attacks. Pritchard, of Glasgow, has reported the case of a patient who was treated in the same hospital for three attacks of scarlet fever occurring within two years.

Stiebel writes as follows: "In the case of a woman, aged about fifty years, I have seen scarlet fever run its complete course four years in succession, the skin desquamating in certain areas in parchment-like pieces a half-shoe in length." Von Jürgensen, who quotes Stiebel, remarks, "From the latter circumstance I take the case to be a genuine one."

To our minds the regular periodicity of these attacks and the exfoliation of large sheets of epidermis point most strongly to the attacks having been of the nature of "erythema scarlatiniforme" of the exfoliative type and not true scarlatina.

The same statement applies to the case reported by Jahn of a woman who had seven attacks, and to that of Henrici of a woman who is said to have had sixteen attacks of scarlet fever.

As showing the comparative frequency of multiple attacks of the infectious disease, the figures of Mycelius, quoted by Sternberg, are interesting:

	Second attacks.	Third attacks.	Fourth attacks.	Total.
Smallpox	505	9	0	514
Scarlet fever	29	4	0	33
Measles	36	1	0	37
Typhoid fever	202	5	1	208
Cholera	29	3	2	34

From this table it would appear that multiple attacks of scarlatina are less common than of the other exanthemata.

Körner,[1] who has made a careful study of scarlatina recurrences, came to the conclusion that second attacks were rather more severe than first attacks. He mentions 8 cases in which the second attack was fatal. The first attacks commonly occurred in childhood before the age of ten years and the second attack from two to six years later, although in 6 cases a second attack occurred within a year.

Recurrent Eruptions and Relapses.—Considerable confusion has arisen in literature concerning the proper classification of secondary scarlatinal eruptions. It is well known that the exanthem of scarlet fever may, in rare instances, disappear and recur in a few days; it is manifestly improper to regard the reappearance of the eruption under such circumstances as a true relapse. Again, after complete convalescence from scarlatina the eruption of scarlatina and other symptoms may appear for a second time. It is somewhat difficult to set a definite time limit before which recurrences are to be regarded as relapses and after which they are to be looked upon as second attacks.

Reasoning from analogy with the relapses of typhoid fever, we might regard as a *relapse* in scarlatina a redevelopment of several or all of the more important symptoms of the disease, occurring either during the course of the illness itself or immediately after the completion of convalescence. Cases recurring some time after convalescence has been established ought to be regarded as second attacks.

Relapses are, in all likelihood, due either to a reawakened activity of the scarlet-fever poison within the body, or to a reinfection from without. Kennan[2] believes that a patient with a mild scarlatina placed in a ward with severe cases might later be reinfected. From a study of the literature he thinks relapses are more common than formerly, and attributes the increase to the grouping of cases in special hospitals. True relapses usually occur during the second or third week of the disease.

In the majority of cases the recurrence is quite as complete in its symptomatology as the original attack. Not only does the eruption reappear, but there may be also renewed fever, vomiting and sore throat. In other cases the first or the second attack may be rudimentary and poorly developed and may complement each other. The recurrence commonly runs a shorter and milder course and usually ends favorably; that this is not invariably so is instanced by the statistics of Körner, who noted a fatal termination in 8 cases of second attack.

Richardson gives an interesting account of a large number of relapses on board the frigate "Agamemnon." During an outbreak of scarlatina 300 out of 800 men were attacked. The ship was then thoroughly disinfected and aired for a month. Of 102 convalescents who returned to the ship, 18 developed relapses within five days. The disease, however, was also recorded in many of those who remained on land. The

[1] Ueber Scharlach recidive, Jahrb. f. Kinderh., 1875 and 1876, vol. **9**.
[2] Dublin Jour. Med. Sci., 1898, No. 324.

second attacks were in some cases mild, but in others as severe as the original disease.

Relapses developing immediately after scarlatina and second attacks within four or five weeks have been reported by Bartels, Barthez and Rilliet, Faye, Gaupp, Jenner, Hillier, Kjellberg, Lefevre, Müller, Hall, Peacock, Richardson, Röbbelen, Schwarz, Smith, Solbrig, Steinbeck, Steinmetz, Steinhall, Stiebel, Trojanowsky, Wood and others.[1]

Before accepting a secondary eruption as a true relapse the possibility of its being a septic rash must be eliminated. These septic eruptions are often spotted in character, but may at times closely resemble the true eruption of scarlet fever. The rosebud eruption associated with protracted fever, referred to by Thomas as a pseudo-relapse, is probably of this nature.

In very rare instances a *second relapse* may occur. Such a case has come under our observations, the temperature chart of which is reproduced (Fig. 97).

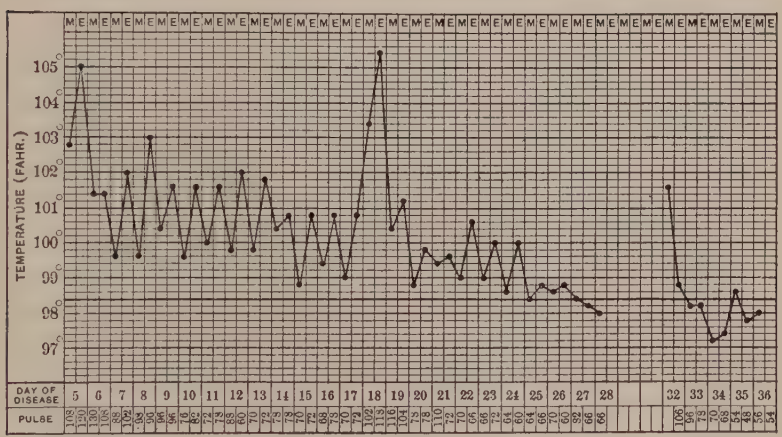


FIG. 97.—Scarlet fever; two relapses. A. D., aged twenty-one years.

A. D., an Italian, aged twenty-one years, was admitted to the Municipal Hospital on June 9, 1892, on the fifth day of an attack of scarlet fever. He had a well-marked rash, sore throat and high fever. The evening temperature on the day of admission was 105° F. On the ninth day there was well-pronounced desquamation. The temperature hovered between 99° and 101° F. until the eighteenth day, when it rose to 105° F. Accompanying this rise there were headache, abdominal pain and diarrhea and a recurrent, very bright rash; no throat symptoms. Urinary examinations were negative. Three days later a second desquamation began. The temperature now gradually declined, reaching normal on the twenty-seventh day of the disease.

[1] Quoted by Thomas: Loc. cit., English translation, Ziemssen's Encyclopedia, p. 190.

The patient was believed to be well, when on July 6th, or the thirty-second day of the disease the temperature again rose to 101.8° F. The patient complained of a slight sore throat, and a rash, followed by a fine desquamation, appeared on the face, arms and trunk. The temperature declined quite promptly; the patient made a good recovery and was discharged from the hospital on July 26th.

It is seen that the first relapse occurred upon the eighteenth day of the disease, and the second upon the thirty-second, or just two weeks later.

COMPLICATIONS AND SEQUELÆ OF SCARLET FEVER.

Throat.—Angina is an essential feature of the symptomatology of scarlet fever and cannot be regarded as a complication except where it is excessively developed. The most moderate expression of the scarlatinal sore throat is a uniform congestion of the uvula, anterior pillars and tonsils. This form has been designated as *erythematous angina*. In more severe cases the mucous membrane is greatly swollen, and there is extension of the catarrhal inflammation posteriorly to the pharyngeal wall and anteriorly over the soft palate; these parts are of a deep-red color and bathed in a profuse mucoid secretion. The swelling of the soft palate may be so intense as to seriously interfere with swallowing and to cause the regurgitation of liquids through the nose. The tonsils may also exhibit great increase in size and embarrass both deglutition and respiration.

In the *membranous* variety of angina the mucous membrane of the tonsils is covered with an exudate, which is usually of a yellowish or brownish tint and thinner and softer than the membrane of true diphtheria. While in most cases the pseudo-membranous deposit is limited to the region of the tonsils, it is not uncommon for it to be present upon the half-arches and also scattered in patches upon the soft palate. It may likewise spread by way of the pharynx into the posterior nares and, in rare cases, to the tongue and buccal mucous membrane. Extension of the process along the Eustachian tube gives rise to inflammation of the middle ear, a most frequent complication of anginose scarlet fever. The glands about the angles of the jaw undergo inflammation and tumefaction and commonly suppurate. Pronounced constitutional symptoms accompany this variety of the disease. The temperature hovers about 104° or 105° F., and there is marked disturbance of the nervous system. Intense restlessness, delirium, stupor, coma or convulsions may be present. The pulse is extremely frequent, often reaching 140 or 150 beats per minute. There is profound prostration, the urine contains albumin and the patient is completely overwhelmed by the poison of the disease.

When there is extension of the process to the *nose* a purulent rhinitis is set up. There is a profuse discharge of a thin muco-purulent and often blood-stained material, frequently containing shreds of mem-

brane. This irritating discharge inflames the nostrils and the upper lip and gives rise to impetiginous sores. The nose is swollen and the nostrils obstructed, causing considerable difficulty in breathing. An offensive odor is given off which can be detected some feet from the bedside. The nasal inflammation is attributed to the action of the streptococcus, the extension of whose pernicious activity may give rise to infection of the nasal sinuses.

French writers have called attention to the bad prognosis in these cases of early purulent coryza. The mortality in the Aubervilliers Hospital was over 50 per cent, and this complications was feared more than the most malignant forms of angina.

The membranous inflammation may extend to the *larynx* and produce serious difficulty in respiration. As has already been stated, however, laryngeal involvement is extremely rare in scarlet fever.

In normal scarlatina the larynx is exempted, and the mucous membrane, being in a healthy state, is not particularly susceptible to the noxious influence of the streptococcus or the diphtheria organism. In measles, on the other hand, the larynx is primarily involved and the soil is rendered favorable for the implantation of these microörganisms.

The *gangrenous* variety of angina is fortunately rare, and is, for the most part, observed in hospitals. The gangrene may begin upon the tonsils, at the site of the rupture of an abscess. The necrotic process may involve the entire tonsil, which sloughs out *en masse*. In some cases the gangrene is limited to the tonsillar tissues; in others it spreads beyond, attacking and destroying the palatine arches, the uvula and a considerable portion of the soft palate. The affected parts are at first covered with a grayish-black, pultaceous deposit, which, when thrown off, discloses to view frightful loss of tissue. The odor emitted from these cases is foul and penetrating. The nose and ears are commonly involved and give exit to an ichorous discharge. The glands of the neck are greatly swollen; the constitutional depression is profound. In our experience the most common form of gangrenous angina has been characterized by circumscribed necrosis of the soft parts, particularly the soft palate, leading to irregular or rounded perforations about $\frac{1}{2}$ inch in diameter. This condition may develop early or may be postponed to the second or third week of the disease. We have observed this complication much more often in mixed cases of scarlet fever and diphtheria than in scarlet fever alone. The prognosis in this circumscribed gangrene is very unfavorable, although patients occasionally recover with considerable deformity of the soft palate.

In extremely rare cases gangrene may commit frightful ravages. The connective tissue of the neck may become involved, the overlying skin destroyed and the muscles and large bloodvessels laid bare. Where the patient does not die of hemorrhage from erosion of the carotid artery, jugular vein or other large bloodvessels, he is sure to succumb to the blighting influence of the septic poisoning. Recovery can only take place where the gangrene is limited to small areas.

Secondary Angina in Scarlet Fever.—The throat involvement thus far described occurs early in scarlatina and influences to a considerable degree the course that the disease takes.

A *secondary angina* may develop late in the disease; indeed, at times after convalescence is established. It is not rare for the tonsils to become the seat of a severe inflammation, increase greatly in size and after a few days undergo suppuration. The neighboring soft palate becomes reddened and greatly tumefied. There is distressing pain, and speech and swallowing are difficult. We have here the usual symptoms of a suppurative tonsillitis or quinsy. In some cases the tonsillitis subsides without pus formation. We have observed these late anginas in hospital wards, a circumstance which suggests a second infection from without as the cause. Similar attacks of tonsillitis have occurred in ward maids and nurses, a fact which renders this view all the more plausible.

Postscarlatinal Diphtheria.—Before the days of bacteriology all cases of membranous angina were regarded as diphtheria. It is now recognized that the membranous deposit frequently seen in the throat early in the course of scarlatina is nearly always due to the streptococcus. Diphtheria is, as a rule, a complication of the stage of convalescence.

Caiger[1] gives the date of onset of 408 cases of postscarlatinal diphtheria:

Time of Onset of 408 Cases of Postscarlatinal Diphtheria (Caiger).

Weeks.	Cases.	Percentage of total cases.
One	11	2.69
Two	36	8.82
Three	55	13.48
Four	77	18.87
Five	54	13.23
Six	46	11.27
Seven	38	9.31
Eight	27	6.61
Nine	18	4.41
Ten	13	3.18
Twelve	9	2.20
Over twelve	15	3.67

It is seen from the above figures that the susceptibility to diphtheria is most pronounced from the third to the sixth week of scarlet fever.

Cases of postscarlatinal diphtheria are much more common in hospital than in private practice. In large hospital wards it doubtless occasionally happens that a secondary diphtheria remains undetected and exposes other patients to the infection. The mortality of mixed cases of scarlatina and diphtheria is, as would naturally be expected, higher than that of primary diphtheria.

There is nothing in the clinical or pathological picture of postscarlatinal diphtheria to distinguish it from primary diphtheria. It is usually limited to the tonsils and adjacent half-arches, although it may exhibit greater extent and spread to the posterior nares or to the larynx. The thick, grayish-white exudate contrasts strongly with the

[1] Scarlet Fever, Allbutt's System of Medicine, p. 161.

thin, smeary, yellowish or brownish deposit seen in the early stages of scarlatina. Paralyses, such as are seen after diphtheria, are excessively rare after scarlet fever. This observation is so well attested that when paralysis occurs after scarlatina there is a reasonable ground for the suspicion that a mixed infection has been present.

The diagnosis will, in large measure, rest upon the bacteriological findings. The presence of the Klebs-Loeffler bacillus in a throat which is the seat of exudate indicates the existence of diphtheria.

Since the specificity of the diphtheria bacillus has been established, numerous examinations of scarlatina throats have been made to determine the character of the membranous angina. Chabade,[1] of St. Petersburg, made cultures of 214 scarlatinal throats; of these, 98 had a catarrhal angina, 33 had a lacunar angina with a pseudo-membrane in the tonsillar crypts, and 83 had a pseudo-membranous angina involving the tonsils and adjacent soft tissues.

In the catarrhal group no diphtheria bacilli were found, but streptococci and, at times, staphylococci were present. In the lacunar anginas the Klebs-Loeffler bacillus was found twice. In the pseudo-membranous cases the diphtheria organism was found 11 times, 3 times almost in pure culture and in 8 cases associated with the streptococcus.

Variot and Devé[2] examined the throats of 525 cases of scarlatina. Of this number 62 had exudate in the throat, 30 of which proved to be true diphtheria.

Garret and Washbourn,[3] from cultures of the throat of 666 patients treated in the London Fever Hospital from 1896 to 1898, found that over 1 per cent showed Klebs-Loeffler bacilli on admission.

For many years we have made cultures of all scarlatina patients admitted into the Philadelphia Hospital for Contagious Diseases. The cultures were made at the home of the patient, in the ambulance or after entrance to the ward.

In one series of cases, in which cultures were made after the admission of the patients to the ward, there were 167 diphtheria-negative results and 80 positive, or 32.35 per cent.

In a second series of over 500 cases, in which the cultures were taken either at the home of the patients or immediately after their reception into the ambulance, the results were as follows:

Negative cultures		Positive cultures	
. . .	74	. . .	26
. . .	83	. . .	17
. . .	77	. . .	23
. . .	65	. . .	34[4]
. . .	81	. . .	19
. . .	10	. . .	3
	390		122

Percentage, 23.8.

[1] De l'Association de la scarlatina avec la diphthérie, La semaine méd., 1899, p. 184; Quoted by Northrup in von Jürgensen's article on Scarlatina in Nothnagel's Encyclopedia of Practical Medicine.

[2] Bull. et mém. de la Soc. de hôp., 1900, **17**, 1025. Quoted by Northrup: Loc. cit.

[3] Ann. d. méd. et chir. enfant, 1899, vol. **3**. Quoted by Northrup: Loc. cit.

[4] 1 not recorded.

A further series of 500 cases, some cultured before admission to the wards and some shortly after, gave the following figures:

Negative cultures		Positive cultures	
. . .	87	. . .	13
. . .	84	. . .	16
. . .	80	. . .	20
. . .	86	. . .	14
. . .	80	. . .	20
	417		83

Percentage, 19.9.

The aggregate of these figures gives a total of 1259 cases, of which 285, or 29.25 per cent, yielded diphtheria-positive cultures.[1]

The throats in many of the positive cases showed merely evidences of catarrhal angina. Subsequent cultures in the positive cases would at times be negative, but in not a small number of instances 3 or 4 positive cultures were obtained. There were comparatively few patients in whom the diagnosis of diphtheria would have been made from the clinical appearances.

The diphtheria patients are treated in a building which is quite apart from that occupied by scarlatina patients. Mixed cases are treated in the same building, but in a distant wing.

Ears.—Inflammation of the middle ear is, perhaps, the most common complication of scarlet fever.

Its frequency varies with the character of the epidemic and with the age of the patient. In the anginose variety of scarlatina middle-ear disease follows in almost every case. Some epidemics appear to be characterized by a much smaller incidence of ear complications than others. Holt mentions the fact that in an epidemic occurring in the New York Infant Asylum in the spring and summer of 1889 there were 73 cases of scarlet fever and not one developed otitis. In a fall and winter epidemic in the same institution, two years later, of 43 cases of scarlet fever, 20 per cent developed otitis. The frequency of otitis in different epidemics is influenced by the degree of angina present, and also to some extent by season, middle-ear trouble being more prevalent in the colder months. Infants are more liable to develop otitis media than children of more advanced years. This may be due to the relatively large size of the Eustachian tube in infancy.

Finlayson states that otitis was present in 10 per cent of 4397 cases of scarlet fever reported by him. Caiger[2] analyzed 4015 cases of scarlatina, and determined that otitis media with discharge took place in 11.05 per cent thereof. Burckhart reports this complication in 33 per cent of cases. In attacks with severe throat involvement otitis occurs, according to Holt, in fully 75 per cent of cases.

Bader and Guinon[3] report 33 per cent involvement in the form of

[1] These cultures were examined and reported upon by the City Bacteriological Laboratory.

[2] Scarlet Fever, Allbutt's System of Medicine, New York, 1897, **3**, 150.

[3] Moizard: Scarlatine, Traité d. mal. de l'enfance, Paris, 1897, vol. **1**.

mild or catarrhal otitis and purulent otitis in but 4.5 per cent of cases of scarlatina.

Middle-ear disease results from direct extension of inflammation from the naso-pharynx and doubtless through the action of the bacteria, chiefly the streptococcus. This complication may develop at any time during the course of scarlet fever, even as late as during convalescence. It is apt to develop early in bad cases with severe throat involvement. In 18 cases of otitis media closely observed by us the discharge appeared upon the following days:

Day of Scarlet-fever Illness Upon Which Eighteen Cases of Otitis Media Developed.

	Cases.		Cases.
6th day	1	18th day	1
8th "	1	19th "	2
9th "	2	20th "	1
10th "	1	21st "	1
11th "	1	22d "	1
13th "	1	23d "	1
16th "	1	32d "	1
17th "	1	35th "	1

One or both ears may be affected; when both are attacked the discharge does not, as a rule, appear simultaneously, an interval of four or five days or a week separating the two attacks.

When the ear complication develops early in the course of the disease, while the temperature is high and nervous manifestations still present, the symptoms thereof are apt to be obscured by the general condition of the patient. When the otitis appears at a later date, after the scarlatinal fever has declined, its development is accompanied by a sharp rise of temperature. The fever is usually preceded by pain, although this symptom is extremely variable.

Infants will often carry their hands to their ears and utter sharp shrieks. In some cases there is enlargement and tenderness of lymphatic glands about the ear. The otitis may be a simple *catarrhal* inflammation, or it may be *purulent or suppurative*. In the former variety the duration of the affection is much shorter and of a less serious character. The fever, pain and tenderness subside rapidly after spontaneous rupture or incision of the tympanic membrane.

Purulent otitis media pursues a much more protracted course. A muco-purulent discharge may continue for weeks or, indeed, the condition may lapse into a chronic suppurative otitis. The immediate dangers associated with this condition are extension of the purulent inflammation to the mastoid cells or meninges of the brain, the erosion of bloodvessels, with the production of serious hemorrhages, and finally the development of septicemia or pyemia.

Cases are on record in which the *erosion of large bloodvessels* has led to fatal hemorrhage. Baader[1] reports the case of a boy, aged three

[1] Acute Verblutung bei Scharlach, Cor.-Bl. f. schweiz. Aerzte, 1875, vol. 5.

years, suffering from a purulent otitis complicating scarlatina, who developed on the eleventh day of the disease a severe and uncontrollable hemorrhage from the ear which caused death on the third day. Autopsy disclosed a perforation of the posterior wall of the tympanic cavity and an erosion of the lateral sinus.

Hessler[1] records a case in which a fatal hemorrhage resulted from ulceration of the carotid artery.

A similar case is reported by Hynes,[2] in which a sudden and unlooked-for hemorrhage poured from the right ear in a child aged four years. The child later vomited blood in large quantities and died. It was thought that the bleeding came from the internal carotid artery.

Hüber[3] reports a case of hemorrhage from an eroded vessel which caused a hematoma of the neck, the opening of which resulted fatally. Kennedy has reported 3 fatal cases of hemorrhage, and Möller and West each 1 instance.

The following case of *septicemia* associated with purulent otitis was observed by Dr. Welch in the Philadelphia Hospital for Contagious Diseases in 1889:

F. F., a boy, aged thirteen years, was admitted to the hospital on February 2, with a bad anginose scarlet fever. His condition improved for a week, the temperature reaching normal. On February 10th the patient had a chill with a rise of temperature to 104.6 F. On the following day another chill and a temperature of 107.4° F. The next day the temperature rose to 107.8° F. For a period of ten days there occurred the most violent rises and falls of temperature, the extreme limits being 95.8° and 107.8° F., an excursion of 12°. Chills recurred each day, and on one occasion repeated vomiting. The ear which was discharging was kept throughly clean with a carbolized solution. By February 27th the patient had recovered sufficiently to leave his bed (Fig. 98).

The immediate dangers of purulent otitis having been passed, there remain severe structural changes which may seriously interfere with the sense of hearing. There may be partial or complete loss of the tympanic membrane upon one or both sides; occasionally the ossicles are destroyed and thrown off. Ulceration and necrosis of the walls of the tympanum may occur, with the development of further complications to which reference will be made later. The *labyrinth* may be attacked in rare cases. Pye, Phillips[4] and others have reported cases in which labyrinthine structures were necrosed and discharged *en masse*. These patients were, of course, left completely deaf. Bezold[5] gives the results of 185 cases of scarlatinal otitis: "In 30 there was entire destruction of the membranous tympani, with the loss of one or more bones; in 59 the perforation comprised two-thirds or more of the membrane; in 13 there were smaller perforations; in 44 there were

[1] Quoted by Forcheimer: Loc. cit.
[2] Ibid.
[3] Deutsch. Arch. f. klin. Med., vol. 8, 422.
[4] Quoted by Holt: Loc. cit.
[5] Ibid.

granulations or polypi; in 15 there was a total loss of hearing on one side, and in 6 of the cases on both sides; in 77 of the cases the hearing distance of low voice was less than 20 inches."

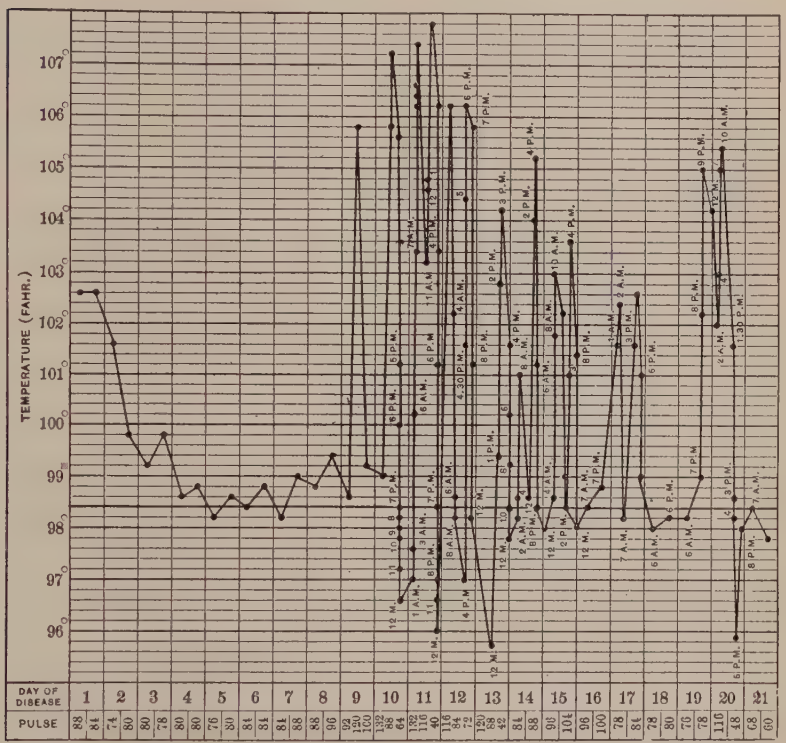


FIG. 98.—Remarkable excursions of temperature due to suppurating otitis media. F. F., aged thirteen years, admitted to hospital in critical condition; bad throat and mouth; ears discharging on second day of disease. Various rises of temperature accompanied by chills; ultimate recovery.

Burckhardt-Merian[1] reported 85 cases of ear complications of which 72, or 84.7 per cent, involved both ears. Of 4309 cases of acquired deafness and dumbness, 445, or 10.3 per cent, were due to scarlet fever. May, of New York, has collected similar statistics; of 5613 cases of deaf-mutism, 572 were traceable to attacks of scarlet fever.

Purulent otitis may, in rare cases, give rise to disease of the *mastoid antrum*. This may occur during convalescence from scarlet fever or may develop after the otitis has become chronic. The mastoid region is painful and tender and acquires a characteristic appearance—the great postauricular swelling causing the ear to stand out prominently from the head. The temperature rises to 103° or 104° F., and, unless

[1] Ueber den Scharlach in seinen Beziehungen zum Gehörorgan, Volkmann's Samml. klin. Vorträge Chir., No. 54.

there is operative interference, brain symptoms may manifest themselves. On incision a mastoid abscess is found present. At times a superficial abscess is found in the region of the mastoid, without actual involvement of the mastoid cells.

Thrombosis of Lateral Sinus.—Thrombosis of the lateral sinus is occasionally encountered in cases in which cerebral abscess or meningitis subsequently develops. The onset is sudden, with chills and high and irregular fever.

Facial Palsy.—Facial palsy is by no means a rare complication of scarlatinal otitis. We have observed this paralysis in a number of cases of severe middle-ear disease. It is due to an extension of inflammation from the tympanum to the facial nerve, where it passes through the roof of the cavity. The symptoms do not differ essentially from facial palsy occurring from other causes.

Abscess of the Brain.—Abscess of the brain may result from extension of the suppurative inflammation from the middle ear. The petrosquamous suture being patulous in children, an avenue of infection to intracranial structures is readily offered. The periosteum of the tympanum is continuous with the dura mater, and extension of inflammation may occur along this membrane. In addition, the infection may be carried to the brain through the medium of the veins.

Purulent Meningitis.—Purulent meningitis is an extremely serious complication that may arise from a suppurative otitis. It may have its origin in thrombosis of the lateral sinus or may develop from necrosis of the roof of the tympanic cavity. There are usually high fever, stiffness of the neck, retraction of the head, vomiting, and, at times, paralytic eye symptoms. Death occurs ordinarily in about a week. The following case will illustrate the symptomatology of this complication:

W. J., aged three years, was admitted to the Philadelphia Hospital for Contagious Diseases on April 9, 1903, with a severe attack of scarlet fever. On the sixth day of the disease the right ear discharged. Fever was protracted, the temperature not touching normal until the thirtieth day. Later the temperature rose as the result of a cervical abscess. There was no fever from the forty-fourth to the fifty-fourth day. At this time the temperature began to rise and the patient vomited. He cried out sharply upon being disturbed. A gradually increasing stuporous state developed. The neck was rigid and the head retracted. The pupils were equal and reacted to light. The patient gradually lapsed into complete coma. The temperature rose to 106.6° F., and the patient died on the ninth day of the complication and the sixty-fourth day of the scarlet fever. When the skull was opened at autopsy a foul odor was immediately noticed. A purulent exudate was found covering the entire base of the brain, but involving chiefly the left side. The pia mater under the left cerebellum was infiltrated with pus, and there was free pus in the various fossæ. There was no discoverable caries of the petrous portion of the temporal bones,

and on opening these no pus could be detected. Cultures from the purulent material demonstrated the presence of the Staphylococcus pyogenes aureus.

Complete Deafness.—Complete deafness not due to middle-ear disease occurred in a boy, aged five years, at the Philadelphia Hospital for Contagious Diseases, during convalescence from a well-marked attack of scarlet fever. The patient had been out of bed for a number of days, when he was suddenly taken ill with high fever, vomiting, heavily coated tongue and delirium. This was shortly followed by pronounced mental hebetude; vomiting persisted for several days, nothing being retained upon the stomach. Mental dulness continued for several days, after which, upon the clearing up of the mental faculties, it was noticed that the patient was absolutely deaf. There had not been any discharge from the ears nor any other evidence of otitis. The mastoid region was normal. The temperature for a week or ten days was markedly irregular, fluctuating rapidly between 99° and 104° F. About the same time that deafness was noted there was a paralytic strabismus. The patient left the hospital absolutely deaf. The internal ear was doubtless diseased in this case, perhaps as the result of a localized meningitis.

Eyes.—In cases of severe scarlet fever, particularly where there is a purulent rhinitis, extension of the inflammation may take place and a severe conjunctivitis set up. More often the conjunctivitis that develops is of a mild character, with injection of the bloodvessels of the sclera and lids, increased lachrymation and photophobia.

The *lachrymal duct* and *gland* may become involved through the infection that has its origin in a purulent coryza. Through this channel other ocular structures may subsequently be attacked.

Primary Keratitis.—Primary keratitis with its unfortunate train of symptoms develops at times, particularly in scrofulous subjects. We recall a corneal ulcer in a colored child, who had previously suffered from keratitis, in whom perforation with prolapse of the iris occurred. Leichtenstern reports 2 cases of corneal ulcer and 1 of hypopyon keratitis occurring in a severe epidemic in the hospital at Cologne. Thomas quotes Schröter as saying that the cornea may be affected primarily and independently, usually in the way of rapidly progressing abscesses or suppurating ulcers or pernicious keratomalacia, in which the cornea of one or both eyes, without any marked symptoms, becomes turbid in a few days, is transformed in its totality into a turbid, dirty, grayish-white membrane and exfoliates piecemeal. The inflammatory process may travel thence over the uveal tract and cause a panophthalmitis.

Choroiditis.—Choroiditis may, in rare cases, complicate scarlet fever. In the epidemic already alluded to Leichtenstern saw a case of choroiditis which ended in phthisis bulbi.

In those cases in which a severe nephritis is present ophthalmoscopic examination may reveal the existence of an *albuminuric retinitis*. Both

eyes are usually equally and simultaneously affected. After a protracted course more or less complete restoration usually results.

Temporary blindness, or *amblyopia*, may complicate the kidney condition; after some days complete vision is usually restored. We have personally observed such cases. Porter[1] saw a young girl with severe complications, develop temporary blindness with exophthalmos from infiltration of the cellular tissue of the orbit. Duval[2] saw a similar case of exophthalmos lasting ten days, the sight being subsequently fully restored.

We have observed in the Philadelphia Hospital for Contagious Diseases 2 cases of *orbital cellulitis* complicating scarlet fever and leading to a fatal termination. These cases were seen and studied by Dr. Burton K. Chance,[3] surgeon to the Wills Eye Hospital, Philadelphia, to whom we are indebted for careful notes of the cases:

Case I was a boy, aged seventeen years, who during a protracted convalescence from a severe scarlet fever developed a sudden diffuse cellulitis of the right orbit. A chill and sharp rise of temperature were followed by an effusion of fluid into the areolar tissue, with protrusion of the globe. The eyelids were red and excessively edematous. The fundus was at first pale, but later intensely red, with fine hemorrhages. There was marked swelling of the disk, an overdistention of the veins and contraction of the arteries. A day or two before death the cornea became necrotic and the eye was lost. High fever, delirium and coma preceded death, which took place one week after the development of the complication. The examination of the orbital structures after death revealed only a diffuse serous infiltration; there was no evience of intraocular suppuration.

Case II was a boy, aged ten years, who was convalescing from scarlet fever, when there developed in the right orbit an acute congestion with infiltration of the tissues, producing proptosis between the intensely edematous lids. The local symptoms were similar to those in the first case. Throughout the course of the process the cornea remained unaffected. Deep incisions were made into the periocular tissues, evacuating a quantity of blood-tinged serum, but no pus. On the eighth day after the onset of the complication the patient was seized with convulsions and died. Permission to make an autopsy was refused.

In rare cases failure of vision may be due to atrophy of the optic nerve or to detachment of the retina. *Optic neuritis* may occur with meningitis or without such involvement, as in a case reported by Putnam.

Heart.—The heart may suffer in scarlet fever from (1) the scarlatinal tinal toxin; (2) as a result of nephritis; (3) from secondary infections, such as rheumatism, pyemia, etc.

[1] Quoted by Thomas. [2] Ibid.

[3] Dr. Chance reported his findings in a paper read before the Philadelphia County Medical Society, May 27, 1903. This was published in Am. Med., June 13, 1903, p. 960.

That the scarlatinal poison has a direct influence upon the heart is seen in the early tachycardia, the heart-beats being out of all proportion to the temperature. Furthermore, in malignant cases that are overwhelmed at the onset by the poison of the disease the symptoms are those of an acute cardiac failure; the pulse is rapid, small and irregular; the extremities are cold, and pallor and cyanosis are often present. In severe cases of the disease the scarlatinal toxin, according to Romberg,[1] may early cause a pronounced *dilatation of the heart.*

The occurrence of nephritis in scarlet fever naturally leads to changes in the cardiac muscle. Whenever the kidney involvement is at all pronounced there will be found a *hypertrophy and dilatation of the heart.* The changes are apt to be present upon both sides, but the preponderant enlargement is nearly always found upon the left side.

Riegel[2] states that in most, if not in all, cases of scarlatinal nephritis there is an increased arterial tension from the very beginning. After the blood-pressure has persisted for some time the heart enlarges as a consequence. In some cases the increased size of the heart may be noticed a few days after the onset of the nephritis. It is readily seen how this form of cardiac disease is produced. The development of nephritis by raising the arterial tension throws an extra burden upon the heart; if the heart has already been injured by the influence of the scarlatinal poison, the strain may be too much and acute dilatation may result. If the heart muscle has more recuperative power a compensatory hypertrophy may take place.

If the left heart develops a pronounced insufficiency a dilatation of the right side will usually occur. When this results we see the usual symptoms of cardiac insufficiency—dyspnea, rapid pulse, enlargement of the liver, etc. A murmur may or may not be heard over the mitral orifice. It is impossible to recognize the fact that the bruit is not due to an endocarditis, but to cardiac dilatation. This murmur will be found to disappear as the heart improves.

Myocarditis. Myocarditis is the heart condition which is most frequently called into existence by the scarlatinal toxin and by the associated nephritis. The other forms of heart disease are more commonly associated with secondary rheumatism or septic infection. Ashby found *endocarditis* not uncommon with rheumatoid affections developing in the third or fourth week of scarlet fever, but not with the early synovitis.

Roger[3] has found endocarditis an uncommon complication. Out of 2213 cases of scarlet fever (1727 in adults) examined by him, he saw but 2 cases of endocarditis. On the other hand, he noted extracardial murmurs 692 times.

[1] Ueber die Erkrankungen des Herzmuskels bei Typhus Abdominalis, Scharlach, etc., Deutsch. Arch. f. klin. Med., vol. **49**, 369, 413.

[2] Ueber die Veränderungen des Herzens, etc., bei Acuter Nephritis, Ztschr. f. klin. Med., 1884, **7**, 260. Quoted by von Jürgensen: Loc. cit.

[3] Loc. cit., p. 941.

McCollom,[1] in an analysis of 1000 cases of scarlet fever, says: "A mitral systolic murmur was detected in 187 cases; *bruit de galop* in 5 cases; irregular action of the heart in 54 cases; endocarditis in 3 and pericarditis in 5 cases." Many of the murmurs referred to were thought to be due to lack of tonicity of the heart muscle as a result of action of the scarlatinal poison.

Von Jürgensen expresses the opinion that endocarditis of the cardiac wall is more common in scarlet fever than valvular involvement. He further believes that this mural endocarditis may slowly extend to the valves after the attack of scarlet fever is over.

Pericarditis.—Pericarditis occurs from time to time in the course of scarlet fever, being much more common in association with nephritis, synovitis and pyemia than with cases of simple scarlatina. Roger has observed cases of dry pericarditis, both at the height of the disease and during convalescence.

In pyemia endocarditis and pericarditis are commonly present; the exudate in the latter affection in such cases may be purulent. Roger saw a child, aged eight years, with a severe scarlet fever complicated by a purulent otitis media, die on the forty-seventh day of the disease. At autopsy the pericardium was covered with a false membrane; there was an ulcerative endocarditis and an abscess in the wall of the left ventricle. The streptococcus was recovered from these lesions.

In our own experience severe cases of endocarditis have been rare, and, when present, have been accompanied by joint involvement. We recall a boy, aged twelve years, who during the third week of scarlet fever had articular swellings which recurred from time to time for several weeks. He also had a well-marked albuminuria. This patient developed at a later period an endocarditis which severely damaged the mitral valve; he subsequently exhibited a presystolic murmur with a pronounced thrill over the mitral region. The murmur had a peculiar crowing sound of a musical character. After undue exertion he developed a sudden dilatation of the heart with rapid pulse and a change in the character of the murmur which now became blowing. He was tided over this crisis, but a few weeks later he again developed a cardiac dilatation and died. A rather unusual symptom in this patient was a *geographic erythema* which appeared over the trunk from time to time, recurring apparently with fresh joint involvement and then gradually fading away.

In another fatal case we observed a vegetative endocarditis attacking the mitral and aortic valves, associated with pleurisy, joint swellings and extensive purpura.

Lymphatic Glands.—A generalized enlargement of the lymph glands constitutes a part of the normal symptomatology of scarlet fever. The subcutaneous lymph nodes in all parts of the body undergo some hyperplasia, but those situated in the neighborhood of the facial

[1] Scarlatina, Med. and Surg. Repts. Boston City Hosp., 1899.

orifices undergo the greatest tumefaction. That this *primary* lymphatic involvement is due to the scarlatinal infection is evidenced by the fact that the lymphoid elements of the spleen, liver and intestines become likewise hyperplastic.

It is only when the lymph glands become excessively enlarged or undergo suppuration that a complication is added that augments the danger of the disease.

The most aggravated cases of lymphadenitis occur in association with the anginose variety of scarlet fever.

FIG. 99.—Greatly swollen and suppurating maxillary glands.

In these cases the glands at the angle of the jaw undergo rapid enlargement, causing the head to be thrown backward. This complication increases the suffering and danger of the child, who by this time is already prostrated by the poison from a sloughy throat and discharging ears and nose. The temperature is high, the nervous system markedly disturbed and death imminent.

By the fifth or sixth day of the disease the maxillary glands may already have attained the size of small apples. They are hard at first, but gradually break down and suppurate.

In cases of scarlet fever of less severity, but accompanied by pronounced angina, it is not at all rare for the glands at the angle of the jaw to enlarge and suppurate. In cases terminating favorably the gland after incision becomes gradually drained of pus in the course of a few weeks and heals up. One or both glands may suppurate, the process being simultaneously bilateral in the bad cases. It is rare for

any other glands to undergo suppuration early in the course of the disease, save in the malignant cases presently to be described.

The connective tissue of the neck may, in large part, become the seat of a *diffuse cellulitis* which develops during the first or second week in connection with great glandular intumescence in severe cases. This frightful condition, known as Ludwig's angina (*Angina Ludovici*), is fortunately rare, for it is almost inevitably fatal. The neck is diffusely swollen, often from the clavicles to the chin and parotid region; instead of the natural concavity of this region the induration makes of the curve a straight line.

The head is forced back by this extensive brawny infiltration. The neck is hard, indeed often board-like to the touch, and of a bluish-red color. There may be great difficulty in breathing, owing to the unnatural position of the head and pressure upon the larynx. The constitutional symptoms accompanying this condition are those of a profound septicemia; the fever is high and irregular and often associated with chills and sweats. The pulse is rapid and feeble, and the prostration great. Death may occur before suppuration of the infiltration takes place. In other cases suppuration occurs, with extensive destruction of tissue. A fatal result may occur from pressure upon the air passages or from edema of the glottis. In other cases extensive burrowing of pus may take place, the purulent fluid finding its way into the thorax, as in the cases reported by Henoch and Bartels. Cremen[1] saw the pharynx perforated, the food coming out through the opening.

One of the most dangerous consequences of the extensive suppuration is erosion of the large veins of the neck. Baader reports 2 cases of fatal hemorrhages after extensive suppurating cellulitis. The first occurred in a boy, aged four years, during the fourth week of a scarlet fever complicated by pharyngeal diphtheria. A huge swelling extended from the jaw-bone to the larynx on the left side. This was incised to relieve suffocative symptoms. Instead of pus, blood clots were removed, after which a thick stream of arterial blood issued forth, which was checked by compression. Four days later a fatal hemorrhage occurred from the nose and mouth. The autopsy showed that the external carotid artery had been destroyed by gangrene.

In the second case, a child, aged six years, developed Ludwig's angina on the thirteenth day of scarlet fever. This was incised below the clavicle; profuse hemorrhage later occurred from this wound. Autopsy showed a large opening in the external jugular vein, where it had been eroded by the suppurative process.

A form of *late glandular involvement* is not uncommon in the course of scarlet fever. This takes place after the fever and acute symptoms have subsided, not infrequently occurring during convalescence. The glands at the angle of the jaw and the submaxillary lymphatic gland are those usually affected. There is moderate enlargement of the

[1] Quoted by Thomas.

gland, which becomes quite hard and somewhat tender. Suppuration may occur, but more commonly the gland gradually decreases in size and resumes its normal dimensions.

Retropharyngeal Abscess.—Retropharyngeal abscess may occur as the result of the burrowing of pus from suppurating glands. Bokai[1] observed this complication 7 times in 664 cases of scarlet fever in children. In 6 of these cases the abscess was attributed to an adenitis of the retropharyngeal glands. In a fatal case this complication was seen as early as the fifth day of the disease.

Kidneys.—No exanthematous disease is so frequently complicated by inflammation of the kidneys as scarlet fever. It is rare for a severe attack of this disease to run its course without the development of albuminuria. The frequency of renal complications varies very greatly in different epidemics; at one time albuminuria with dropsy is a striking feature of the prevailing type of the disease, while in other epidemics it is rare to observe this complication. In general terms it may be stated that severe epidemics of scarlatina are more apt to be accompanied by nephritis than the mild ones.

Divergent opinions have been expressed from time to time as to the *cause* of the scarlatinal nephritis. Steiner claimed that nephritis was a part of the symptomatology of the disease, just as much, indeed, as the rash was. The great frequency of this complication in scarlet fever and certain peculiarities in the clinical picture have led some writers to regard the nephritis as a specific entity peculiar to this disease. It is true that the clinical course presents features which, to a certain extent, differentiate nephritis in scarlet fever from this affection occurring under other circumstances. The great tendency to anasarca, which is particularly evident in certain epidemics, the onset of the complication at a rather uniform period, and the favorable outcome in cases presenting most alarming symptoms, give to scarlatinal nephritis a rather characteristic clinical picture. Moreover, the pathological changes are of a quite uniform character, the essential condition being an acute glomerulo-nephritis.

Forchheimer pertinently remarks, however, that almost identical changes may be produced in the kidney by the administration of toxic doses of cantharidin. It must also be remembered that many acute infectious diseases are complicated by the development of nephritis, and this is particularly true of those maladies in which we have a secondary infection with streptococci; for instance, in smallpox. In a careful analysis of the urine of 128 cases of smallpox we found albuminuria in, 65 per cent and tube casts in 45 per cent of the cases.

Albuminuria may appear *early* in the course of scarlatina; that is, during the first week of the disease. This albuminuria is usually *transient*, not lasting more than one or possibly two days. It, moreover, seldom gives rise to any definite symptoms. Inasmuch

[1] Jahrb. f. Kinderh., vol. **10**, 108. Quoted by von Jürgensen: Loc. cit.

as it is usually coincident with high fever, it is regarded as a *febrile albuminuria.*

It should be remembered, however, that this albuminuria is not merely functional, but is due to an acute degeneration of the tubules of the kidney, the result, doubtless, of the elimination of toxins.

Some authors refer to an early suppression of the urine; when this occurs it is nearly always a manifestation of severe nervous disturbance.

The nephritis that occurs early does not, as a rule, give rise to uremic symptoms, nor does it lead of itself to a fatal termination. In severe cases of scarlet fever that terminate early in death, structural alterations may be found in the kidneys, in common with the changes in the liver, spleen, heart and other organs.

Postscarlatinal Nephritis, or Nephritis of Convalescence.—It is after the subsidence of the acute symptoms that the true scarlatinal nephritis is prone to develop. Most of the cases will be found to begin during the third week of the disease. We have seen albuminuria appear for the first time as late as the sixty-third day, and it may even develop at a later period.

Below is appended a series of 61 cases of albuminuria specially studied among 150 cases of scarlet fever:

Albuminuria in Scarlet Fever; Day Upon Which Sixty-one Cases of Albuminuria Were First Noticed.

Case.	First noticed.		Case	First noticed.	
1	3d day	Transient	32	17th day	Lasted 23 days
2	4th "	Transient	33	17th "	Lasted 4 days
3	4th "	Transient	34	17th "	Transient
4	5th "	Transient	35	19th "	Lasted 9 days
5	6th "	Transient	36	19th "	Lasted 21 days
6	6th "	Transient	37	19th "	Transient
7	7th "	Transient	38	19th "	Persisted
8	7th "	Transient	39	20th "	Transient
9	7th "	Transient; reappeared on 25th day	40	20th "	Lasted 18 days
10	8th "	Transient	41	21st "	Transient
11	8th "	Transient	42	21st "	Transient
12	8th "	Transient	43	21st "	Lasted 17 days
13	8th "	Transient	44	22d "	Transient
14	9th "	Transient	45	22d "	Transient
15	10th "	Transient	46	23d "	Transient
16	10th "	Transient	47	23d "	Transient
17	10th "	Transient	48	23d "	Lasted 17 days
18	10th "	Transient	49	25th "	Persisted
19	11th "	Transient	50	28th "	Transient
20	11th "	Transient	51	28th "	Transient
21	12th "	Transient	52	29th "	Transient
22	12th day	Lasted 8 days	53	32d "	Transient
23	13th "	Transient	54	33d "	Transient
24	14th "	Transient	55	34th "	Transient
25	14th "	Transient	56	36th "	Transient
26	14th "	Transient	57	36th "	Transient
27	14th "	Transient	58	37th "	Lasted 6 days
28	14th day	At intervals until 56th day	59	39th "	Transient
29	15th "	Lasted 10 days	60	41st "	Transient
30	16th "	Lasted 15 days	61	63d "	Lasted 6 days
31	17th "	Transient			

It will be seen upon reference to the above table that almost all of the cases of albuminuria observed during the first two weeks of the disease were transient, lasting but a day or two. In many of the early cases but a trace of albumin was found. None of the patients in this series had anasarca or any severe uremic symptoms. It is proper to add that these cases occurred at a time when the type of scarlet fever was quite mild.

As has already been stated, the frequency of nephritis varies strikingly in different epidemics. Roger gives an interesting analysis of the occurrence of albuminuria in 2157 cases of scarlet fever in adults and children:

	Men.	Women.	Children.
Number of patients	718.0	1009.0	430.0
Fatal cases (with albuminuria)	16.0	23.0	14.0
Patients cured (having had albuminuria)	264.0	308.0	91.0
Total number of cases of albuminuria	380.0	331.0	105.0
Frequency of albuminuria per 100 patients	38.9	33.1	24.8
Frequency of albuminuria per 100 cured	37.6	31.2	21.8

It will be seen from these figures that albuminuria is less frequent in children than in adults.

Vogl reports as high an incidence of nephritis in one epidemic as 34 per cent. Cadet de Gassicourt has observed late nephritis in 30 cent of all cases. It was present in 18 per cent in a series of cases studied by Friedländer. Baginsky has recently reported 88 cases of nephritis among 919 cases of scarlet fever (a percentage of 9.57) observed in the hospital during a period of five years.

Ashby states that the average of several years in hospital cases under his observation was 6 per cent. In a series of 2078 cases Caiger reports acute nephritis in only 3.32 per cent. The wide discrepancy in these figures may be due, to some extent, to the standards adopted in interpreting the presence of nephritis, but wide variations are not uncommon in different epidemics. Holt states that the average is from 6 to 10 per cent.

Age.—Hetzka, of St. Petersburg, has compiled statistics of 138 cases of nephritis occurring in children in the Elizabeth Hospital; these figures indicate that children under two years of age are very much less apt to develop nephritis than those above the age of two or three:

	Cases.	Nephritis, cases.	Per cent.
Under 1 year	25	1	4.0
Between 1 and 2 years	107	5	4.6
2 and 3 "	106	12	11.3
3 and 4 "	79	16	20.2
4 and 5 "	80	20	23.2
5 and 6 "	89	18	21.9
After 6 "	300	60	16.6

While severe cases of scarlet fever are more apt to be followed by nephritis than mild cases, it is impossible in any individual instance to predict the development or the non-occurrence of this complication,

because the scarlatinal attack may be severe or mild. There appears to be something in the individual make-up which predisposes one toward or protects one against a complicating nephritis. Doubtless each individual has certain organs or tissues which are more vulnerable to the noxious influence of the scarlatinal poison than others.

The opinion formerly held, that "catching cold" plays any important role in the etiology of nephritis complicating scarlatina, is being discredited by most writers on the subject.

Symptoms of Nephritis.—In some patients albumin appears in the urine for the first time during convalescence; in other cases albuminuria is a reawakening of the nephritic process that manifested itself early during the acute stage of the disease.

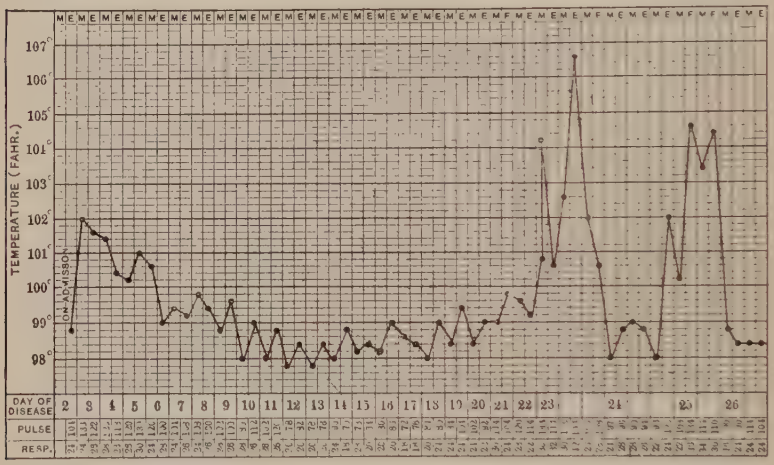


Fig. 100.—Scarlet fever. F. O., aged six years. Chart showing pronounced rise of temperature coincident with the onset of albuminuria. Albumin was first found on the twenty-third day.

The nephritis with its accompanying symptoms of intoxication ordinarily comes on insidiously, although in some instances it may explode with alarming suddenness. The development of albuminuria is accompanied or often preceded by a rise of temperature. A febrile elevation in the third week of scarlet fever will commonly be found to be due to nephritis. The character and duration of the fever are extremely variable. It may persist for a number of days or may drop to normal at the end of forty-eight or seventy-two hours. The temperature often exhibits striking irregularities, dropping to normal and suddenly rising again. Ordinarily the pyrexia is moderate in intensity, but it may rise to great height. We have seen a temperature of 106.6° F. accompanying a moderate albuminuria which appeared on the twenty-third day of the disease and disappeared on the twenty-sixth day (Fig. 100). In severe nephritis fever may persist throughout

the duration of this complication. In some cases no fever is noted whatsoever.

Before appearance of the albumin there is not infrequently noted a considerable increase in the quantity of the urine voided. As a result of this polyuria urination is frequent and may wake the patient from his sleep at night.

Most writers refer to pain in the back as one of the early symptoms of scarlatinal nephritis; this lumbar pain cannot be frequent or severe, at least in children, for it is most rare to hear a complaint in reference thereto. Hematuria may be one of the early symptoms to direct attention to the kidneys.

One of the most characteristic features of scarlatinal nephritis is the *marked pallor of the countenance, with puffiness* of the eyelids. In walking through a scarlet-fever ward one may frequently pick out the nephritic patients by noting this appearance. *Edema* is a particularly common symptom in scarlatinal nephritis. A peculiarity of this complication is the tendency to rapid anasarca. This appears to be much more common in the nephritis of scarlatina than in ordinary Bright's disease. In explanation of this it is stated that the edema is due not alone to the condition of the kidneys, but also to the changes in the lymphatics and bloodvessels of the skin.

The anasarca is accompanied by a pale or alabaster-like appearance of the skin. The swelling usually begins about the eyelids and the ankles, but later the legs, genitalia and lower portion of the abdomen become affected. In severe cases the entire body may be attacked. A thin and poorly nourished child may become rapidly metamorphosed into a plump child within a few hours, as a result of the edematous infiltration. Anasarca, according to Trousseau, is met with in cases of medium severity, rather than those of the most serious forms of scarlatina. Its frequency varies greatly in different epidemics. Barthez and Rilliet observed anasarca in one-fifth of their cases. Some writers have stated that nearly all of their cases were dropsical. Among the 150 cases of scarlet fever referred to above, we did not see a single instance of anasarca, although edema of the face was not an uncommon symptom.

Anasarca may affect deep-seated structures or the serous cavities. The fluid may fill up the peritoneal cavity, giving rise to a pronounced ascites, or the pleural or pericardial sacs may be similarly infiltrated. The soft palate, uvula, epiglottis and aryteno-epiglottidean ligaments are more rarely attacked, in the latter case giving rise to edema of the glottis. In such cases intubation or tracheotomy may have to be performed to prevent suffocation.

Edema of the lungs and brain are extremely apt to be present in cases that terminate unfavorably.

Anasarca may be present in rare cases without albumin being found in the urine. This does not indicate that nephritis is not present, for uremic symptoms may burst forth suddenly and with great intensity.

Henoch reports the case of a child, aged twelve years, admitted to the hospital and edema of the face and scrotum following scarlet fever. The urine was scanty, but contained neither albumin nor nephritic elements. Two days later convulsions occurred and three days afterward the child died.

The Condition of the Urine.—In the so-called febrile albuminuria, the urine contains albumin for a day or two, after which it disappears, perhaps to reappear at the end of the third week. Microscopic examination reveals the presence of cylindroids and occasionally a few hyaline or epithelial casts. Not infrequently red and white blood corpuscles are present. A cloudiness is often seen in the urine, which is due to the presence of mucus resulting from the presence of degenerated epithelium. With the advent of the true scarlatinal nephritis the urine, as a rule, begins to decrease in quantity, although exceptionally there may be for a short time an increased secretion. The urine becomes quite concentrated and contains an abundance of urates, which give a pronounced ring with the nitric acid test. Albumin is found at first in small quantity, but later in larger amount. In bad cases it may constitute one-half by bulk with the heat test or, indeed, there may be complete coagulation of the urine. At this time hemorrhage from the parenchyma of the kidney may take place, causing the urine to look brownish-red and smoky. Under the microscope will be seen red blood corpuscles, cylindroids, epithelial detritus and hyaline, epithelial, fatty and blood casts.

When there is much blood present it will settle as a deep-red collection at the bottom of the urine glass. The amount of albumin is corresponsingly increased with an augmentation in the quantity of blood.

Exceptionally albumin may be absent for a number of days, although casts are present; on the other hand, a considerable quantity of albumin may be present without urinary casts being found.

The specific gravity varies greatly according to the amount of urine passed. It may be as low as 1004, or as high as 1040 or more; ordinarily it will be between 1020 and 1035. The amount of urine secreted progressively diminishes in severe cases, and there may be complete suppression for a period of twenty-four hours or longer. Cases in which this occurs usually succumb.

The reaction of the urine is almost invariably acid. The quantity of urea excreted varies with the amount of urine, but is usually under 2 per cent.

When dropsy occurs the urine is extremely scanty, high colored, of high specific gravity and contains an abundance of albumin and casts.

It is not at all uncommon for the albumin to disappear every now and then from the urine, only to reappear in a few days. We have frequently noted this irregularity in scarlatinal albuminuria. In certain cases the albumin appears intermittently in the urine. At other times it is absent at certain periods of the day; this peculiarity has been

observed in a considerable number of patients in certain epidemics. This occurs independently of those cases in which albumin is absent while the patient remains in a recumbent position, but reappears when a sitting or standing position is assumed.

These observations make it a matter of importance to carefully examine the urine at frequent intervals. If an examination is made only from time to time albumin, which is intermittently absent or which disappears at a certain time of the day, may be completely overlooked. It is a good plan to examine the urine every other day up to the fifteenth day of the disease and then to make daily analyses. The urine should be examined both for albumin and microscopically, and the amount passed and the specific gravity should be ascertained. With the use of very delicate tests small quantities of albumin will doubtless be found which are not recognizable by the usual tests employed. For practical purposes, however, the nitric acid or heat test will suffice.

In cases that tend toward recovery the urine increases in quantity, the blood and casts disappear and the albumin gradually diminishes.

In our experience the urine in scarlet fever has given a positive *diazo reaction* in about 25 per cent of the cases examined. This reaction has little or no diagnostic value.

Aubertain[1] and Roger have each reported cases of scarlatinal albuminuria in which albumin was absent in the mornings while the patient remained in bed, but would appear soon after the patient stood upon his feet. Ten minutes' standing posture in one case would produce an albuminuria lasting about two hours. Exercise in the horizontal position failed to excite the presence of albumin. In some of these cases of *orthostatic albuminuria* a gradual cure takes place; others eventuate in a permanent albuminuria.

In some cases of severe nephritis, particularly when the urine becomes greatly reduced in quantity, symptoms of *uremia* are prone to develop. These usually come on gradually after distinct evidences of kidney involvement, although this is not invariably the case. Indeed, uremia may, in rare cases, supervene without the previous existence of albuminuria. Henoch reports such a case: On the twelfth day of scarlatina, in a child, aged four years, intense right-sided convulsions and stupor developed; examination of the urine on the previous day had failed to show albumin. The patient was catheterized on the development of the symptoms, and a considerable quantity of albumin was then found.

Ordinarily the first symptoms in a patient about to develop uremia are vomiting and, at times, diarrhea. This is doubtless an effort on the part of Nature to eliminate some of the retained poisons through these channels. Leichtenstern claims that one of the most frequent modes of onset of scarlatinal uremia is the development of pronounced

[1] L'Albuminurie orthostatique au cours de la néphrite scarlatineuse, La presse méd., 1901.

dyspnea associated with rapid heart action. There is usually some elevation of temperature, which, in bad cases, may become excessive and reach 106° or 107° F. But the symptoms referable to the nervous system dominate the clinical picture. There are frequently intense headache, tinnitus aurium and somnolence or stupor, with occasionally sudden loss of vision. These symptoms are rapidly followed by convulsions. The convulsive movements may be partial, that is, limited to one set of muscles, as those about the jaws, in which event there may be a tonic contraction; in other instances they are unilateral or general, affecting the entire body. When the convulsions are limited to certain sets of muscles consciousness is usually preserved, but when there is a general epileptiform seizure it is followed by coma, at least for a time. The convulsive attacks may be of brief duration, lasting but a few minutes, or they may persist for an hour or more. There may be a single seizure, although more commonly there is a succession of convulsions upon the same or successive days.

When the convulsions are severe and protracted death may result from exhaustion, cerebral hemorrhage or edema of the lungs. In other cases a fatal termination comes on later, the patient lapsing into a progressively deepening coma. In some cases a gradual oncoming stupor may be the only pronounced symptom of uremia.

In favorable cases the convulsions cease, the stupor disappears, the urine increases in quantity and the patient emerges from the crisis.

The amaurosis which develops from time to time in uremia usually disappears when the convulsions cease, but the blindness may continue for several weeks, ultimately ending in complete recovery. In some cases aphasia and hemiplegia may develop during uremic convulsions and disappear when convalescence is established.

In rare instances patients may become *maniacal* after uremic attacks. Wagner[1] saw a patient who had eleven convulsive seizures, each one being followed by the wildest mania; although the temperature registered 107.6° F., the patient recovered.

Melancholia may also develop as a sequel of uremia.

If the urine now increases in quantity, there is but little likelihood of a recurrence of the severe nervous manifestations. The abnormal urinary constituents gradually disappear from the urine and the patient is entirely restored to health.

Prognosis.—The prognosis of scarlatinal nephritis is much more favorable, both as to life and to functional restoration of the kidneys, than would be expected from the nature of the symptoms. The vast majority of patients recover from the nephritic attack, even where alarming uremic phenomena have been present. Intense and unremitting headache, protracted convulsions, repeated vomiting and coma are symptoms of bad omen. The quantity of albumin in the urine is no reliable guide, as a severe nephritis may exist with but little

[1] Quoted by von Jürgensen: Loc. cit.

albumin in the urine, and the converse may also be true. The number and character of the casts, and particularly the quantity of the urine, are more important criteria. Suppression of urine renders the situation extremely grave, although recovery may take place if diuresis can again be established.

The opinion has prevailed for a long time that scarlatinal nephritis was but seldom followed by chronic Bright's disease. While it is fortunately true that *restitutio ad integrum* usually takes place, it is nevertheless certain that the number of cases of permanent nephritis following scarlatina has been much underestimated.

We had at the Municipal Hospital, during the winter of 1902, a girl, aged eight years, who was brought in with a well-marked case of scarlatina from a hospital where she was being treated for nephritis, said to date from an attack of scarlet fever five years previously. She had bloody urine for some days, but made a good recovery from the scarlatina and left the hospital many weeks later still suffering from a chronic nephritis.

Aufrecht[1] reports a case of nephritis after scarlet fever lasting twenty years, and terminating in a contracted kidney. Leyden, Litten, Forchheimer and others have reported cases eventuating in chronic Bright's disease. Holt says that he formerly believed such results rare, but larger experience has convinced him that this sequel is not uncommon. Of 77 cases of scarlatinal nephritis occurring in the Southwestern Hospital of London, in 1892, 6 cases, according to Caiger, were discharged with chronic albuminuria after a prolonged residence.

If delicate tests for albumin were employed and careful microscopic examination of the urinary sediment were uniformly made for months after attacks of scarlatina, it would doubtless be found that a larger proportion of cases eventuate in chronic nephritis than has been supposed.

Many of these patients have structurally damaged kidneys, which at some future period, as a result of a variety of causes, may be reawakened into activity. The practical lesson to be borne in mind is that the urine of patients convalescent from scarlatinal nephritis should be carefully examined from time to time and the diet and mode of life regulated accordingly.

Scarlatinal Rheumatism (Synovitis Scarlatinosa).—The attempt to distinguish between a scarlatinal synovitis and a complicating rheumatism is scarcely warranted by our present knowledge of the subject. Synovitis and arthritis occurring in the course of scarlet fever are frequently associated with other phenomena, such as endocarditis, pericarditis, pleurisy, etc., which are common rheumatic complications.

The frequency of joint involvement in scarlatina appears to vary in different countries and in different epidemics. Trousseau says: "By minute interrogation, and by carefully examining and applying a cer-

[1] Deutsch. Arch. f. klin. Med., 1887, **42**, 517.

tain degree of pressure to the joints, articular pains are found to be present in about one-third of the cases (of scarlatina). It is important to know this; for acute affections of the joints, general arthritis, pericarditis and endocarditis frequently occur during the course of the disease."

Ashby observed synovitis to occur 20 times among 900 cases of scarlet fever. Koren,[1] of Christiana, noted scarlatinal synovitis of a mild type 27 times in 426 cases (6.3 per cent) of scarlet fever in the epidemic of 1875–1877.

Vogl appears to have observed an unusually large number of cases of joint complications in scarlatina. He is authority for the statement that articular involvement occurred in 13.6 per cent of the cases in the epidemic of 1884–1885, and in 10.6 per cent in 1894–1895.

Hodger[2] say 217 instances of scarlatinal synovitis among 3000 cases of scarlet fever, or 3.2 per cent.

It is seen from the above figures that the frequency of this complication varies from about 3 to 13 in 100 cases. Our personal experience would lead us to regard the first figure (3 per cent) as representing more nearly the average incidence of this complication.

Two forms of joint involvement are recognized—a simple serous synovitis and a purulent or suppurative arthritis. The mild form is fortunately far more common than the suppurative variety. Articular involvement may occur at any period of the disease, but is most common during the stage of desquamation in the second or third week of the disease. The wrists and fingers are the joints most often attacked, although the ankles and toes not infrequently participate in the process. Sometimes the larger joints, such as the shoulders and knees, become involved. The usual symptoms are pain, stiffness and swelling. Redness may or may not be present. Trousseau states that scarlatinal rheumatism is usually mild and of short duration, is commonly localized, and when it disappears does not tend to return. We have seen cases in which there were periods of disappearance and of recurrent involvement. Scarlatinal arthritis is frequently, although not always attended with a rise of temperature which commonly reaches 101° or 102° F.

In mild cases the articular inflammation subsides in the course of three to five days. In more severe cases it may last for weeks.

Suppurative Arthritis.—Suppurative arthritis is a rare complication of scarlet fever, and usually occurs late in the course of the disease. The joint becomes painful, swollen, hot and reddened; the fever is high, the patient prostrated and all of the usual symptoms of pyemia are present. One or several articulations may be involved. In the vast majority of cases a fatal termination supervenes. In rare instances, through surgical intervention, or even at times without, recovery takes

[1] Johannsen: Loc. cit., p. 195.
[2] Eichorst's Spec. Pathol. und Therap., 1897, p. 241.

place after a long and tedious illness, but with serious impairment of the functional activity of the joints involved.

We have seen scarlatinal rheumatism associated in one case with a severe endocarditis and a recurring geographic erythema of the trunk and extremities, and in another case with endocarditis, pleurisy and hemorrhagic purpura.

In persons of scrofulous habit a scarlatinal synovitis may, after a long course, eventuate in tuberculosis of the joint (white swelling).

In rare cases of scarlet fever the sheaths of tendons may undergo inflammation (*tenosynovitis*), which commonly terminates in suppuration. In other cases periarticular abscess, may occur and rupture into one of the large joints.

Cases of *periostitis* and *osteitis* have been reported, involving particularly the petrous portion of the temporal bone, the nasal bones and the cervical vertebræ.

Bruck[1] describes a form of scarlatinal myositis, which attacks most commonly the lumbar, pectoral, abdominal and intercostal muscles and which is characterized by pain and soreness and moderate rise of temperature.

Purpura Hæmorrhagica.—It is important to distinguish between true hemorrhagic scarlatina and secondary purpura developing during the course of the disease. The former condition appears, as a rule, at the outset, and is characterized by constitutional symptoms of great intensity and malignancy, associated with hemorrhages into the skin and from the mucous membranes.

Purpura hæmorrhagica comes on usually after the subsidence of the acute scarlatinal symptoms and not infrequently during convalescence. Most cases develop during the second or third week, and most commonly from the fourteenth to the twentieth day. The patient loses appetite, is apathetic and may have some rise of temperature. Nose-bleed is often one of the first symptoms; soon pin-head-sized purpuric spots appear upon the skin of the trunk, extremities or face; the gums become swollen and bleed; the urine contains blood, and hemorrhage may take place from the stomach and bowels. A marked pallor soon develops, the patient becomes prostrated and, in severe cases, death takes place from loss of blood, hemorrhage into the brain or exhaustion.

Albuminuria is usually present, even when the urine is free of blood.

In mild cases the hemorrhages from the various mucous membranes cease after a short time, and the patient, although intensely anemic, recovers.

These secondary purpuras are not seen alone in scarlatina, but in other infectious diseases, such as influenza, rheumatism, smallpox, etc. They are probably due to some secondary infection which destroys either the integrity of the blood or the vessel walls. We have seen 2 cases of hemorrhagic purpura complicating scarlatina.

[1] Petersb. med. Presse, 1896, No. 18.

A child, aged three years, suffering from a well-marked scarlatina, developed late in the course of the disease swelling of the joints, diffuse ecchymotic patches upon the face, trunk and extremities and endocarditis. The patient after some days' illness died. Autopsy showed vegetations upon the mitral and aortic valves, a right-sided pleurisy and hemorrhages into the mediastinal and peritoneal cavities.

FIG. 101.—Purpura hæmorrhagica associated with pleurisy, endocarditis and joint trouble, scarlet fever. Fatal termination.

The second case was a girl, aged eight years, who, upon the seventeenth day of a scarlatina of average severity, became apathetic, had slight rise of temperature and nose-bleed. The following day, small, pin-point petechiæ appeared upon different parts of the body, bleeding occurred from the gums, and an abundance of blood was found in the urine. The bleeding continued for a few days, but ceased under treatment and the patient made a good recovery. A pronounced anemia persisted for a few weeks. Albuminuria was present even after the cessation of hematuria.

Although this complication is uncommon, a number of cases have been published. Biss[1] reports the case of a boy, aged three and half years, who suffered from a severe attack of scarlet fever complicated by double otitis media. On the nineteenth day after admission to the hospital he developed an extensive eruption of pin-point hemorrhages over the trunk and limbs, vomited $\frac{1}{8}$ pint of blood, passed a similar quantity by the bowel and rapidly succumbed. Autopsy showed the kidneys to be "transformed almost entirely into fat."

Murray[2] saw a colored child, aged two years, develop scarlatina after

[1] Lancet, August 2, 1902, p. 286.

[2] Case of Scarlet Fever with Purpura, Lancet, February 11, 1893, vol. i.

an operation for hernia. On the ninth day of the attack there occurred bleeding from the kidneys, bowels, stomach, nose and gums, and hemorrhages into the skin and conjunctivæ. The red corpuscles numbered 2,000,000 per cubic millimeter. Urine contained blood and epithelial and hyaline casts. Death took place on the fourteenth day.

De Boinville[1] places on record the case of a boy, aged four and a half years, who, on the sixteenth day of scarlet fever, had hemorrhages from the nose and hemorrhagic spots on the scalp and about the knees. Although the amount of blood lost was small, the epistaxis could not be checked and the patient died five days later.

Phillips[2] reports the case of a girl, aged fourteen years, suffering from scarlet fever, who had a recurrent rash on the fourteenth day, and swelling of the joints on the twentieth day; six days later petechial patches on the chest and legs and free bleeding from the nose, gums and kidneys. Patient had albuminuria and acute dilatation of heart, but recovered.

Gangrene.—Mention has already been made of the sloughing of the tissues of the neck, which occasionally accompanies cellulitis and abscesses. The muscles and large bloodvessels of the neck may be exposed by gangrene of the overlying skin.

Gangrenous stomatitis, or *noma*, is also seen at times after scarlatina, although it is much rarer than after measles. Apart from these conditions, a form of spontaneous gangrene is, in rare instances, observed during the course of scarlatina. When seen, gangrene usually develops during the second or third week of the disease, and usually attacks the extremities. In most of the reported cases the condition has been attributed to embolism. There appear first bluish discoloration, pain and coldness, and then hemorrhagic extravasation into the skin. In some of the reported cases the gangrene was so deep and extensive as to necessitate amputation of the affected member.

Cases of gangrene have been reported by Blanpain,[3] Hudson,[4] Küster[5] and Chapin.[6]

Wood and Arrigoni[7] have reported cases of gangrene affecting the genitalia, and Wilson[8] a case of gangrene of the face occurring three weeks after convalescence from scarlatina.

Pearson and Littlewood[9] report the case of a boy, aged four years,

[1] A Peculiar Case of Scarlatina Hæmorrhagica, Lancet, August 9, 1903. This case is evidently a case of purpura hæmorrhagica, and not one of true hemorrhagic scarlatina.

[2] Scarlet Fever with Relapse; Acute Rheumatism and Purpura Hæmorrhagica; Recovery, Lancet, 1893, vol. ii.

[3] Scarlatine; gangrene spontneé des membres; embolies; autopsie, Arch. med. Belges, 1869, **9**, 324.

[4] Scarlatina Resulting in Mortification of the Right Limb and Successful Amputation, Trans. Ohio Med. Soc., 1858.

[5] Spontan. Gangrän des Unter-schenkels nach scarlatina; Amputatio Femoris; Tod., Kassel, 1876 and 1878.

[6] An Unusual Result of Scarlet Fever; Embolus; Gangrene; Amputation, Med. Age, 1884, **11**, 205.

[7] Quoted by Thomas.

[8] Reviewed in Arch. f. Kinderh., 1898, p. 418.

[9] Dry Gangrene of Both Legs; Double Amputation, 1897, **2**, 84.

who, after an ordinary scarlet fever, on the eighth day developed small hemorrhagic discolorations of the skin of both legs. In a few days the legs became livid, first upon the feet, thence spreading upward. The femoral pulsation was lost, the legs became cold, intermittent pain occurred and lines of demarcation formed about 3 inches above the knees. At the same time slight dilatation of the heart was discovered. On the twenty-third day of the disease the right leg was amputated, and, a week after, the left. The patient recovered. Embolic and thrombotic clots were found in the bloodvessels of the amputated limbs.

Buchan[1] reports the case of a boy, aged thirteen years, whose scarlatinal rash on the second day exhibited a bluish appearance on the legs. A few days later the veins, especially at the apex of Scarpa's triangle, stood out quite prominently. Hemorrhages occurred into the

FIG. 102.—Gangrene of the skin complicating scarlet fever. Patient developed gangrene of both hands and died.

skin of the legs, particularly the right; there were also hematuria, nose-bleed and hemoptysis. The lower part of the right leg became mummified and a definite line of demarcation formed just above the knee, where an amputation was performed. The patient made a rapid recovery.

We recall a child treated in the Municipal Hospital in 1900, who developed gangrene about the third week of a severe scarlatina. Ecchymotic patches developed upon the leg, followed by rather superficial sphacelation of the tissues. A few days later one hand became blue and cold, and shortly after this the other hand became similarly affected. The radial pulse was lost and both hands assumed an indigo-blue color. Before actual gangrene could take place the child, who was

[1] Lancet, October 5, 1901, p. 915.

greatly prostrated, died. The gangrene in this case was doubtless due to embolism (Fig. 102).

Skin Complications.—Reference has already been made to the various abnormalities of the rash of scarlet fever, including an excessive development of miliary vesicles. It remains to discuss the occasional complicating skin disorders which are quite apart from the scarlatinal process.

Febrile *herpes* occurs every now and then during the invasive stage of the disease. The patches develop usually about the mouth, although they may be situated about the cheeks or ears. While herpes is not very frequent in scarlet fever, it is more commonly seen than in smallpox or measles.

Urticaria is not an infrequent accompaniment of scarlet fever, although it cannot be considered as bearing any special relation to the disease. It may be seen early or late in the course of the illness, and is usually neither extensive nor protracted. This complication is doubtless due to the presence in the blood of some accidental toxin or drug.

Blebs may occasionally develop upon the skin as a result of a coalescence of neighboring miliary vesicles in intense rashes. Thomas says that they may reach the size of hazel-nuts. Bullæ may also occur upon patches which are destined to terminate in gangrene of the skin. Some authors speak of the occurrence of pemphigus, particularly in certain epidemics. These are, in all probability, not true instances of pemphigus, but of bullous dermatitis of septic origin.

We have occasionally seen cases of localized necrosis of the skin in small areas, a condition analogous to the so-called varicella gangrænosa, but better designated *dermatitis gangrænosa*.

Eczema may occur as a complication of scarlatina, but is more apt to develop as a sequel. Intense desquamation may leave the skin dry, harsh and fissured and the seat of eczematoid patches; these may persist for some time after convalescence. In other cases a purulent discharge from the ears or nose may give rise to an impetiginous eczema in the region of these orifices; the skin becomes moist and covered with crusts as the result of the irritating and infective discharges.

Cutaneous abscesses may occur upon any portion of the integument. This complication is uncommon, usually occurring in septic cases. We recall an adult patient in whom a large number of small abscesses occurred in the skin.

Furuncles may develop during an attack of scarlet fever, although they are more apt to appear after the termination of the disease. In a severe case seen by us they complicated an unrecognized and untreated nephritis, after convalescence from scarlatina had taken place.

Phlebitis.—Phlebitis appears to be a rare complication of scarlet fever. The veins of the neck, upper extremities and cranial cavity are those most apt to be affected. The cases in which this complica-

tion develops are usually severe; the phlebitis not uncommonly occurs in the neighborhood of suppurating glands or abscesses.

Cases have been reported by Rees,[1] Hofnagels,[2] von Jürgensen[3] and Moizard and Ulmann.[4] The latter writers were able to collect from the literature but 4 cases of phlebitis after scarlatina. In their own case a phlebitis of the right axillary and humeral veins, cultures demonstrated the condition to be due to a streptococcic septicemia.

Roger[5] published an account of a woman, aged forty-nine years, who died on the eleventh day of a severe scarlatina, after suffering for three days with a phlebitis of the crural vein. Autopsy showed vegetations on the auricular surface of the mitral valve.

Alimentary Canal.—Reference has already been made to the condition of the mouth and throat in scarlatina.

The vomiting, which is so common at the beginning of scarlet fever, is seldom sufficiently intense or protracted to unfavorably influence the course of the disease. In hemorrhagic scarlet fever the material vomited may contain blood. At a later stage of the disease vomiting may be an expression of nephritis, or, when repeated, of an oncoming uremia. Thomas says that severe gastralgia, persistent and often bilious vomiting and great sensitiveness of the stomach to all food occur in some cases; we have never observed such severe gastric symptoms. Pathological changes have frequently been described as occurring in the walls of the stomach, but it would seem that in many cases these do not give rise to pronounced symptoms.

In the period of invasion and the early eruptive stage it is not at all rare for *diarrhea* to manifest itself. In ordinary cases this is due to a simple catarrhal *enteritis* which yields of its own accord or to simple treatment. In very severe cases of scarlatina, however, the bowel movements may be frequent and profuse, and accompanied by pain and tympanitic distention. If the diarrhea is protracted the tongue becomes dry, the eyes sunken and the face pinched. This complication under such circumstances is much to be feared, leading, as it may, to exhaustion and a fatal termination.

Jöel[6] saw a patient in whom severe gastro-intestinal symptoms and high fever were the most conspicuous symptoms; slight angina, subsequent scaling and an attack of scarlet fever in the sister made the diagnosis clear.

In the later stages of the disease there is occasionally encountered a *dysenteric* condition, characterized by frequent, small, bloody or catarrhal stools and painful tenesmus.

Litten[7] speaks of diarrheas of *typhoidal character*. There is marked distention of the abdomen, and critical hemorrhages from the bowel may occur. The stools are liquid, of a pale-yellow color and dotted

[1] Fatal Phlebitis After Scarlet Fever, Lancet, 1862, ii, 63.
[2] Ann. Soc. de méd. d'Anvers, 1848, **9**, 333.
[3] Loc. cit.
[4] La Phlebite scarlatineuse, Arch. d. méd. des enfants, 1899, **2**, 601.
[5] Loc. cit., p. 962.
[6] Quoted by Thomas.
[7] Charité-Ann., vol. **7**, 128.

with whitish specks. This condition is associated with a protracted remittent fever, dry tongue, pronounced apathy and later renal complications. When the patient recovers convalescence is long drawn out. On autopsy in these cases there is enlargement of the spleen and the mesenteric glands, swelling of Peyer's patches and of the solitary follicles, the latter at times exhibiting erosion.

Liver.—The liver is generally increased in size, the inferior border often extending below the false ribs. Hepatic enlargement is, however, not constant, and the liver may, in severe cases, be much diminished in size as a result of degeneration and atrophy. Jaundice is not a common symptom, but it is encountered, according to some authors, with especial frequency in certain epidemics.

Mild jaundice has no special significance, but severe cases may indicate extensive fatty degeneration of the liver.

Roger[1] says that lesions of the liver often explain different forms of delirium and modifications of temperature. He mentions the case of a confirmed alcoholic, aged nineteen years, suffering from scarlatina, who had severe delirium of the type of delirium tremens early in the disease. The liver was large and palpable; the urine was free of albumin. The patient died three days later, with a temperature barely above normal. The liver at autopsy was found to be huge and completely degenerated.

Respiratory Organs.—The larynx may become involved as a result of a second diphtheria or a membranous inflammation of streptococcic origin, although the latter is much rarer than in measles. Edema of the glottis results at times from extension of inflammation and on other occasions from nephritis.

Perichondritis of the larynx is a rare and fatal complication. According to Kraus,[2] it occurs about once in 200 to 250 cases of scarlatina. Rauchfuss saw 4 cases among 903 cases of scarlatina, and Leichtenstern 2 cases among 467 patients. Its development may necessitate the performance of intubation or tracheotomy.

Pulmonary complications are much less common in scarlatina than in measles. The *bronchial tubes* and *lungs* are nevertheless, according to Henoch, much more frequently involved in bad cases than is generally believed. These lesions are masked by the severe constitutional symptoms, and are often not discovered until autopsy. In a series of 98 fatal cases of scarlatina, reported by McCollom,[3] 15 were due to bronchopneumonia.

As would naturally be expected, pulmonary complications are commoner in infants than in older children and adults. Roger[4] gives the following morbidity and mortality statistics of pulmonary complication in scarlatina according to age:

Scarlatina.	No. of patients.	Cases of pneumonia.	Mortality.
First infancy	56	6 (10.7 per cent)	5 (8.9 per cent)
Childhood	430	6 (1.3 ")	2 (0.4 ")
Adults	1727	4 (0.2 ")	3 (0.1 ")

[1] Loc. cit., p. 1055.
[2] Prag. med. Wchnschr., 1899, pp. 29 and 30.
[3] Quoted by Corlett: Loc. cit.
[4] Loc. cit., p. 983.

All of the pneumonias in the infants were bronchopneumonias. Four of the children of the second group had bronchopneumonia and 2 had apical pneumonia. Bronchopneumonia occurred in 2 adults.

Bronchopneumonia in severe cases appears usually during the first or second week. Henoch remarks: "We found bronchitis and bronchopneumonia in nearly all the severe cases and also repeatedly during life."

Lobar Pneumonia.—Lobar pneumonia may develop during the height of the disease, or more commonly after nephritis has manifested itself. The upper lobes are more often affected than other parts of the lungs.

Edema of the Lungs.—Edema of the lungs is by no means a rare complication when the kidneys are severely affected and a general dropsy exists. Serous transudation into the lungs may occur rapidly and lead to sudden death.

Involvement of the *pleural cavities* in scarlatina is uncommon. Pleurisy may develop in association with a lobar pneumonia or it may occur independently thereof. The process may be dry or accompanied by serous or purulent exudate; scarlatinal pleurisies show a pronounced tendency to eventuate in *empyema*, a complication which adds much gravity to the disease. However, desperate cases may at times terminate favorably, as is evidenced in a remarkable case of Trousseau, who drew off from the chest of a girl, aged fourteen years, 750 gm. of pus, the patient making a complete recovery.

Thomas says all forms of scarlatinal pleurisy are characterized by rapid development and by but slight local disturbance, even when the affection is very intense. The effusion is usually present only upon one side.

Pleural involvement is more frequent in cases complicated by nephritis. It is especially apt to accompany scarlatinal rheumatism. We have already referred to a patient treated in the Municipal Hospital, who had purpura, endocarditis, synovitis and a fibrinous pleurisy.

Fürbringer regards exudative pleurisy as a frequent complication, occurring, in his experience, in 5 per cent of cases of scarlatina. Johannesen, of Norway, found, among 688 deaths from scarlet fever, but 3 that resulted from pleurisy.

Nervous System.—While the onset of scarlatina is attended in severe cases by pronounced nervous symptoms, these subside if the course is favorable, and do not add to the gravity of the disease. The early cerebral manifestations are in part due to the scarlatinal poison and in part to the high fever. Headache and delirium may be present in ordinary cases, but convulsions and coma presage an attack of great severity.

Later in the disease severe nervous symptoms, such as delirium, convulsions, coma, sudden blindness, etc., may develop as a result of uremia.

Hemiplegia.—Hemiplegia may occur early from a cerebral hemorrhage during the invasive convulsions, or it may come on at a later date as the result of embolism. Taylor[1] reports a right hemiplegia resulting from embolism of the middle cerebral artery; the patient succumbed later to diphtheria.

Addy[2] saw a case of partial hemiplegia with amnesia after scarlatina.

Meningitis.—Meningitis usually results from extension of inflammation and infection from the middle ear or the nasal sinuses. We have already referred to a case of purulent meningitis of the base of the cerebellum which we observed after a purulent otitis media. Roger[3] saw a man, aged twenty-three years, in whom a severe purulent rhinitis complicating scarlatina was followed by meningitis. At autopsy the left frontal lobe of the brain was covered with purulent plaques and the left sphenoidal sinus contained pus. The presence of the streptococcus in pure culture was demonstrated. Similar cases have been reported by other observers. Baudelocque[4] reports a case of meningoencephalitis characterized by headache, vomiting and convulsions, followed by coma and the loss of speech, hearing and sight. Althous[5] reports a case of spinal meningitis with consecutive lateral and posterior sclerosis.

Incomplete Paraplegia.—Cases of incomplete paraplegia have been described by Demange,[6] Roger and others. Roger says that among 2213 patients with scarlatina 4 cases of incomplete paraplegia were observed. Three women had for about a week great difficulty in standing up or walking. The fourth patient was a man who on the second day of the disease had paralysis of the soft palate. Later the two legs and the right arm became affected; the palsy passed off in ten days. Cultures from the throat excluded the possibility of diphtherial infection.

As has already been stated, *facial palsy* occurs occasionally from involvement of the facial nerve in the bony roof of the middle ear.

Insanity.—Insanity has been reported as a complication and sequel of scarlatina. The mental aberration is usually temporary, but may in some cases persist after convalescence. Mitchell,[7] Rabuske and Wagner have each reported attacks of acute mania in scarlet fever, the mania in the last-named case following uremic convulsions.

Carrieu[8] records a case of dementia and Brill a case of scarlatinal insanity with epilepsy. Wildermuth,[9] in a report of 187 cases of epilepsy, states that 12 cases followed attacks of scarlet fever.

Multiple Neuritis.—Egis[10] reports a case of multiple neuritis following scarlatina in which there was an ataxic gait and paralysis of both peroneal nerves. Such cases appear to be very rare.

[1] Med. Times and Gaz., 1880, **2**, 686.
[2] Glasgow Med. Jour., 1880-1885, **13**, 463.
[3] Loc. cit., p. 850.
[4] Gaz. d. hôp., 1837, **11**, 197.
[5] Brit. Med. Jour., 1881, i, 50.
[6] Bull. Soc. anat. de Paris, 1874, p. 503.
[7] Edinburgh Med. Jour., 1881–1882, **27**, 721.
[8] Mew England Med. Month., 1882–1883, **2**, 55.
[9] Quoted by Holt: Loc. cit.
[10] Arch. f. Kinderh., 1900, vol. **28**.

Tetany.—Steffen[1] reports a case of tetany in a young girl suffering from scarlatina; an attack was noticed after each bath. Kühn-Ulsar[2] mentions a case of tetany in a boy, aged four and a half years, suffering from scarlet fever. For six weeks muscular spasms and stiffness were noted, at times limited in extent and at other times general. Trismus was present for fourteen days. The patient gradually recovered.

Bones.—Necrosis of the petrous portion of the temporal bone and of the ear ossicles occurs in severe cases of purulent otitis media. Necrosis of other bones sometimes takes place. Brown[3] reports a case of necrosis of the lower maxilla after scarlet fever, and Weickert[4] reports a case in which both jaws were thus affected.

Neumark[5] reports 30 cases of acute infectious *osteomyelitis*, of which 5 followed scarlet fever.

Sequelæ.—But few words will be devoted to the sequelæ of scarlatina, as they represent merely a continuation of the complications or disabilities resulting from structural damage.

A weakened and anemic state of the system may develop after scarlatina as after many other infectious diseases; the patient is thus lowered in resisting power and rendered more susceptible to the other infectious diseases. There is, however, no such increased susceptibility to tuberculosis as exists in patients recovering from measles.

The various organs of sense may bear for a long time and in some cases forever the marks of a cruel scarlatinal attack. The mucous membrane of the eyes, throat and nose may show persistent pathological alteration.

It is the ears, however, that most frequently exhibit permanent damage. It is largely because of injury to the sense of hearing that scarlatina is so feared by the laity. A chronic purulent otitis media may persist after scarlatina and lead at a remote date to mastoid or intracranial disease. Destructive changes involving the middle ear and the contained ossicles may cause auditory disability, varying in degree from slight impairment of hearing to complete deafness. When this occurs very early in life the loss of this sense may lead to deaf-mutism.

As has already been suggested, the damage to the kidneys is often more than a transitory one. In a certain proportion of cases albuminuria will persist and eventuate in a chronic Bright's disease. In other cases the kidneys are functionally normal, but are rendered more susceptible to subsequent burdens or infections.

Various cutaneous diseases, such as furuncles, eczema, etc., may follow in the wake of scarlatina.

Reference has already been made to certain psychic disturbances, such as mania and melancholia, which may persist after scarlatina.

[1] Jacobi's Festschrift, 1900, p. 83.
[2] Berl. klin. Wchnschr., 1899, No. 39, p. 855.
[3] Lancet, 1844, i, 220.
[4] Deutsche Klinik, 1854, **6**, 22.
[5] Arch. f. Kinderh., vol. **22**.

Chorea.—Chorea may develop a few months after convalescence is established. This sequel is not of great frequency. Carlslaw reports only 3 cases of chorea following 533 cases of scarlet fever, and Priestley[1] 13 cases after 5355 attacks of scarlet fever.

THE PATHOLOGY OF SCARLET FEVER.

Blood Changes.—In scarlet fever but little change has been noted in the *erythrocytes* and *hemoglobin*. Both are apt to undergo slight reduction during the course of the disease and especially if nephritis develops as a complication. In septicemic cases, showing the presence of hemolytic streptococci in blood cultures, the reduction in erythrocytes and hemoglobin is more marked. Rhodin[2] found the *sedimentation-time* of erythrocytes very irregular.

Much more marked and characteristic changes occur in the *leukocytes*. They undergo an absolute increase with an increased percentage of the polymorphonuclear neutrophiles and eosinophiles followed later by a decrease along with an increase of the mononuclear cells and especially of small lymphocytes.

Kotschetkoff[3] states that leukocytosis is influenced by the type of the disease; mild cases show usually from 10,000 to 20,000 white cells; moderately severe cases, from 20,000 to 30,000 cells; the severe and usually fatal cases from 30,000 to 40,000 cells; in some rapidly fatal cases over 40,000 leukocytes were present. Yet Rieder's[4] cases seldom gave more than 20,000 cells, although some were complicated and fatal. Felsenthal[5] found in six attacks of moderate severity in children from 18,000 to 30,000 leukocytes. No change occurs in the prodromal period.

Bowie[6] gives the results of the careful and repeated examination of 167 cases. He concludes that: (1) Practically all cases of scarlet fever show leukocytosis; (2) the leukocytosis begins in the incubation period, very shortly after infection; it reaches its maximum at or shortly after the acme of the disease and then gradually diminishes to normal; (3) in simple uncomplicated cases the maximum is reached during the first week, and the normal generally some time during the first three weeks; (4) the more severe the case, the higher is the leukocytosis and the shorter time it lasts; (5) a favorable case of any variety of the disease has always a higher leukocytosis than an unfavorable one of the same variety; (6) the temperature has no effect on the leukocytosis.

Bowie states that the polymorphonuclear leukocytes are increased relatively and absolutely at first, and then fall to normal; the lymphocytes act in an inverse manner. In simple cases this cycle occurs

[1] Brit. Med. Jour., September, 1897, p. 805.
[2] Deutsch. med. Wchnschr., 1925, **51**, 691.
[3] Quoted by Ewing: Clinical Pathology of the Blood, 1901.
[4] Quoted by Ewing.
[5] Ibid.
[6] Leukocytosis in Scarlet Fever, Jour. Pathol. and Bacteriol., March, 1902.

within the course of three weeks. Kotschetkoff estimates the number of the polymorphonuclears as varying between 85 and 98 per cent, according to the severity of the disease; the highest point is reached on the second day of the eruption, a gradual diminution then occurring.

According to Bowie, the eosinophiles are diminished at the onset of the fever. In simple favorable cases a rapid increase then occurs until the height of the disease is passed, when a gradual decline to normal takes place, the latter occurring after the disappearance of the leukocytosis.

The more severe the case the longer are the eosinophiles subnormal before they rise again. In fatal cases they never rise, but sink rapidly toward zero. Kotschetkoff says that eosinophiles in all but severe cases are normal or subnormal at first; after two or three days they steadily increase, reaching a maximum of 8 to 15 per cent in the second or third week and then decline slowly to normal about the sixth week. The eosinophiles may disappear early in the disease in cases which prove fatal. Essentially similar changes have been more recently reported by Markovitch and Gueratovitch,[1] Lindsay,[2] Bunting and Thewlis[3] and by Trujielo and Garcia.[4] Hickling[5] reports the presence of plasma cells in some cases.

Bowie believes that the simple counting of the leukocytes is of but little *diagnostic* value. A differential count may, however, be of aid, for scarlet fever is one of the few acute infections in which one finds an early increase of the eosinophile cells and a persistence of the increase for some time.

As regards *prognosis* he says: "In simple, severe scarlatina, if the leukocytosis be high and rising, a favorable course may be predicted; if it be low and stationary a tedious course may be expected. If the eosinophiles show a relative increase the augury is good; if they are normal or subnormal after the first day or two, then, in all probability, the case will be severe. The persistence of a relative increase of the eosinophiles suggests some complication, whereas if they come down to normal in the usual manner one may be free from anxiety as regards complications."

Blood Chemistry.—But little has been reported upon blood chemistry changes in scarlet fever. In some cases there is a slight increase of urea nitrogen which may aid in determining the degree of toxicity of the disease, but this is of little or no aid in anticipating kidney changes. When nephritis develops the changes become more marked as observed by Cinca and Nadejde,[6] with an increase of urea nitrogen, non-protein nitrogen and creatinine. The sugar and uric acid usually show no changes, although the plasma chlorides may undergo alteration, and Szirmai[7] states that the cholesterol is usually decreased.

[1] Presse méd., 1925, **33**, 205.
[2] Virginia Med. Month., 1927, **53**, 709.
[3] Arch. Path. and Lab. Med., 1926, **1**, 189.
[4] Rep. d. med. y cir., 1926, **17**, 19.
[5] Jour. Hyg., 1925, **24**, 120.
[6] Compt. rend. Soc. d. biol., 1925, **93**, 389.
[7] Jahrb. f. Kinderh., 1925, **109**, 317.

Wassermann Reaction in Scarlet Fever.—Scarlet fever is one of the diseases in which falsely positive Wassermann reactions have been claimed to occur and a large literature has accumulated upon the subject. In 1911 Kolmer[1] observed only 2 per cent of positive reactions in 250 cases, which was not higher than the expected number due to syphilis. In a more recent study[2] of 30 cases tested from the second day to the sixth week of the disease with his new complement-fixation test, none reacted positively and we believe that it can be stated that scarlet fever alone does not yield positive Wassermann reactions in the absence of congenital or acquired syphilis.

Specific Complement-fixation in Scarlet Fever.—In 1912 Kolmer[3] observed 11.2 per cent positive reactions with antigens of streptococci isolated from scarlet-fever throats; in a subsequent study Dick[4] observed as high as 54 to 88 per cent positive reactions.

With his new test Kolmer[5] has observed over 90 per cent positive reactions with the toxin of Streptococcus scarlatinæ as antigen and from 60 to 76 per cent positive reactions with antigens of the streptococci. These results have given additional weight to the etiological relationship of the organism to scarlet fever, although the occurrence of positive reactions with the sera of some normal individuals containing the antitoxin reduces the diagnostic value of the test for scarlet fever. Villa[6] has recently reported positive reactions, using an extract of scales for antigen, but we have been unable to confirm these results.

THE MORBID ANATOMY OF SCARLET FEVER.

But little information is obtained by postmortem examination in uncomplicated cases of scarlet fever that cannot be foretold by the symptomatology of the disease. The gross morbid changes are usually observed in the skin, tongue, throat and lymphatic structures of the body. Indeed, the most uniform gross alteration is a hyperplasia of all the lymphoid structures of the body.

After death the eruption commonly fades away completely, except in those cases in which the rash has been intense. In the hemorrhagic forms the petechial spots will, of course, remain visible.

Histological Changes in the Skin.—The skin has been studied by a number of investigators, but principally by Klein, Unna and Pearce.

Klein[7] studied the changes in the skin in 20 cases. He found the epidermis slightly thickened, particularly the mucous layer. Many of the rete cells showed dividing nuclei. Between the horny and mucous strata were small spaces containing granules resembling micrococci.

In the rete Malpighii were found lymph corpuscles with deeply staining nuclei. In the corium the epithelial cells of the follicles and

[1] Jour. Exper. Med., 1911, **14**, 235.
[2] Serum Diagnosis by Complement Fixation, Philadelphia, Lea & Febiger, 1928.
[3] Arch. Int. Med., 1912, **9**, 220.
[4] Jour. Infect. Dis., 1916, **19**, 638.
[5] Loc. cit.
[6] Pediatria, 1925, **33**, 1225.
[7] Local Government Report, London, 1876, **7**, 24. Quoted by Pearce: Loc. cit.

sweat glands exhibited an increase of the nuclei. The bloodvessels were distended by corpuscles and occasionally by fibrin. The nuclei of the lymphatics and of the endothelial and muscular coats of the arteries were increased.

Neumann[1] noted swelling of the rete cells and elongation of the prickle cells, between which was evident a cell infiltration, occasionally containing red blood corpuscles. The bloodvessels and lymphatics were dilated. There was slight cellular proliferation around the sweat glands, hair follicles and bloodvessels.

Kaposi[2] regards the changes in the skin as the result of vascular congestion with moderate cell infiltration; the papules and vesicles occasionally seen are due to an excessive exudation and cell proliferation in the papillæ and in the rete mucosum.

Unna[3] examined the skin of 7 cases of scarlet fever. His findings are briefly as follows: There is a marked wrinkling of the whole epidermis along with the papillary body, which is due to an overstretching of the epidermis by the sodden, engorged cutis and to subsequent distortion, after excision of the skin, when the cutis contracts. The elasticity of the cutis indicates that during life it could not have been the seat of edema.

The bloodvessels of the true skin are enormously dilated, suggesting almost distention by artificial injection. This distention, which is present even after death, is the result of a *vascular paralysis*. White blood corpuscles are extremely scant, scarcely more than is found under normal conditions.

No particular changes are found at the height of the eruption in the prickle layer. There is absence of mitosis, edema and of any dilatation of the interepithelial lymph spaces. Mitoses are found first and pretty numerously in the stage of desquamation.

In view of the above findings, Unna regards the changes in the scarlet-fever skin as paralytic and not inflammatory.

Pearce[4] examined the skin in 8 cases between the second and sixteenth days and 1 on the thirty-second day.

On the second day, beyond a congestion of the bloodvessels and slight dilatation of the lymphatics, no changes were observed. In 3 cases examined on the third day a few leukocytes and lymphoid cells were seen in and grouped around smaller lymphatics beneath the rete Malpighii. From the fifth to tenth days the most marked condition was an infiltration of the epithelium with polymorphonuclear leukocytes. The cells apparently leave the bloodvessels beneath the rete and pass up between the epithelial cells and collect in the superficial layers of dead cells, with which they are thrown off. In the connective tissue beneath the epithelium were numerous polymorphonuclear leu-

[1] Med. Jahrb., 1882, p. 152. [2] Path. u. Therap. d. Hautkr., Vienna, 1899, p. 243.
[3] Loc. cit., p. 629.
[4] Scarlet Fever, Its Bacteriology and Gross and Minute Anatomy, Med. and Surg. Repts of Boston City Hosp., 1899.

kocytes and a few plasma cells. The lymphatics were widely dilated and contained many leukocytes. By the twelfth and sixteenth days the leukocytic infiltration had nearly disappeared. In a late desquamating case the rete contained numerous mitotic figures.

Tongue.—When death occurs early in the course of the disease the enlarged papillæ may be visible at postmortem. Pearce[1] made a microscopic study of the tongue in 8 cases, all between the second and ninth days.

The process in the tongue is said to be similar to that in the skin, but is more marked and begins earlier. The chief changes consist of a dilatation of the papillary bloodvessels and lymphatics, a leukocytic infiltration of the epithelial layers, particularly pronounced over the papillæ and the presence of leukocytes in and around the bloodvessels. The polymorphonuclear leukocytes wander between the epithelial cells, collect beneath the superficial epithelium, with which they are cast off. The most pronounced cell infiltration is seen between the fourth and ninth days. Mast cells are increased in number and plasma cells are seen in small numbers about the bloodvessels. Mitoses in the epithelial cells are frequent. Pearce regards the process as inflammatory and suggests that the exciting cause of the leukocytic infiltration may be a positive chemotaxis excited by the presence in the tissues of scarlet-fever toxin, or by substances formed by its action on the superficial epithelial cells.

Lymphatic System.—In 1872 Harley[2] studied the postmortem changes in 28 cases of scarlet fever and concluded that it was a disease of the lymphatic system characterized by hyperplasia of the lymph glands, spleen, tonsils, liver and other lymphatic structures of the body. He, therefore, proposed to substitute for the name scarlet fever the term lymphatic fever.

There can be no doubt that pronounced hyperplasia of the lymphoid tissues is a constant and conspicuous accompaniment of scarlet fever.

Pearce[3] found the mesenteric, retroperitoneal, bronchial and tracheal glands enlarged in all cases. The superficial lymph nodes, such as the cervical, axillary and inguinal, were also found enlarged. The glands were quite firm, and, on section, pale and watery.

Klein and Pearce have both made histological studies of the glands. Klein[4] examined the lymph glands in 8 cases. The centers of the glands were transparent and composed of large cells resembling giant cells. There were also large cells with transparent vesicular nuclei. In the sinuses were small cells and also large granular cells, with one or two transparent nuclei (endothelial).

Pearce studied the glands, including the mesenteric, cervical and bronchial, in 20 cases. The changes observed were similar to those seen in the spleen, but were not present in all cases. The bloodvessels were congested, and in 3 cases small hemorrhages were seen. The

[1] Loc. cit.
[2] Med. Chir. Trans., London, 1872, **60**, 102.
[3] Loc. cit.
[4] Quoted by Pearce: Trans. Path. Soc. London, 1877.

lymph sinuses were dilated and contained many large endothelial cells lying loose in their lumena. These cells were frequently observed to be phagocytic, containing a number of disintegrated lymphoid cells. Plasma cells, exhibiting numerous mitotic figures, were found throughout the lymph nodes.

Spleen.—The gross appearance of the spleen, according to Pearce, permits of a classification into two different groups. There is no increase in pulp, but a marked enlargement of the Malpighian bodies. In such cases the spleen is firm, and the capsule smooth but not tense; on section, there is seen a dark-reddish background, dotted everywhere with regularly or irregularly enlarged Malpighian bodies. This condition was noted in 13 out of 23 cases examined.

In the other class the splenic pulp is greatly increased and the Malpighian bodies indistinct. The spleen is then large and soft. This condition was seen in 7 cases, in 2 of which, however, there was enlargement of the Malpighian bodies. In the remaining 3 cases absolutely no change in the gross appearance of the spleen was visible. The differences described do not seem to depend upon the age of the patient, the stage of the disease, nor the intensity of the infection.

Klein[1] noted in 8 cases examined histologically an enlargement of the Malpighian bodies. A peculiar pale area, composed of endothelial-like cells, was observed in the center of the bodies. The intima of the bloodvessels exhibited a hyaline degeneration, at times leading to obliteration of the lumen.

Pearce made a careful histological study of the spleen in 21 cases. The enlargement of the Malpighian bodies was found to be due to a central massing of large endothelial cells in addition to the presence of numerous plasma cells. These were abundantly present also around the bloodvessels, in the lymphatics and along the trabeculæ. The bloodvessels were greatly congested. A peculiar condition noted was a collection of cells, chiefly plasma and lymphoid cells, but occasionally also a few leukocytes, beneath the endothelial lining of the vessels.

Liver.—The gross changes in the liver are not pronounced. It exhibits usually, although by no means constantly, some degree of enlargement. The consistence is ordinarily less firm than the normal liver. In one case Pearce noted on the surface a number of minute, yellowish areas, which were shown to represent necrotic foci. Roger observed in 2 cases a number of scattered red spots due to subcapsular ecchymosis, a sort of purpura of the liver.

Histologically, the changes in the liver are those of an acute febrile infectious disease. In 22 cases examined by Pearce the liver cells in each instance exhibited the degenerative changes common to fevers. In 4 cases distinct fatty degeneration was noted, and in 7 cases extensive fatty infiltration. An infiltration of lymphoid cells with a few polymorphonuclear leukocytes was found around the portal vessels in

[1] Quoted by Pearce.

11 cases. A few eosinophiles and plasma cells were seen, the latter more particularly in the bloodvessels. Phagocytic endothelial cells were found in the bloodvessels in 5 cases. Focal necrosis of the liver was observed in 4 cases. The focal areas seemed to arise from endothelial cells, derived in part from the capillary endothelium of the liver, and, in part, from embolism through the portal circulation of cells originating in the spleen. The changes are similar to those described by Mallory as frequently occurring in the liver in typhoid fever.

Roger and Garnier[1] made histological examinations of the liver in 12 cases. The changes described by them are of different types: One series concerns the mesodermic elements of the liver—leukocytic infiltration, thickening of the capsule of Glisson, etc., inflammation of the vessels; the other affects the epithelial tissue. The first stage of inflammation in the liver is leukocytic infiltration of the portal spaces. Later, the epithelial cells are altered; they may merely show unequal coloration of the nuclei or they may degenerate in considerable number around the portal spaces, or, finally, a number only may degenerate, forming a limited focus which may subsequently become infiltrated with leukocytes. At the same time inflammation of the conjunctive tissues may increase and the cells present may undergo hyaline and fatty degeneration or fatty infiltration. When parenchymatous hepatitis is extensive the interstitial changes also become pronounced.

Gastro-intestinal Tract.—The mucous membrane of the pharynx, tonsils, and soft palate show, under the microscope, the usual changes observed in inflammation of these structures.

Fenwick[2] described changes in the mucous membrane of the *stomach* analogous to the desquamation of the cutaneous surface; in severe cases there was an absolute loss of epithelium. In addition he found a dilatation of the bloodvessels and a filling up of the gastric tubules with a granular and fatty material and small cells.

Crooke, in a study of 6 cases, found catarrhal gastritis in all, and in the severe cases interstitial and follicular gastritis characterized by hyperplasia and necrosis of the lymph follicles, and infiltration of the muscular coat with round cells. Hesselwarth found 21 instances of severe gastro-enteritis among 81 autopsies.

Pearce examined the stomach histologically in 6 cases. In a case dying upon the second day the surface of the stomach was covered with a thick layer of mucus and necrotic epithelial cells, containing numerous leukocytes and cocci. Polymorphonuclear leukocytes and granular material were found in the tubular glands, and numerous plasma cells between the tubules. Enlarged and altered lymph nodules were seen in the lower part of the mucous membrane; 4 other cases showed similar but less-marked changes.

The *intestines* exhibit changes very similar to those seen in the

[1] Des modifications anatomique et chimique du foie dans la scarlatine, Rev. de méd,. March 10, 1900. Roger: Les maladies infect., p. 1056.

[2] Medico-Chir. Trans. London, 1862, vol. 47.

stomach. Virchow described marked hyperplasia and swelling of the lymph follicles. Crooke says that Peyer's patches at times look like those found in typhoid fever during the first week.

Bone-marrow.—Pearce[1] examined the bone-marrow in 11 cases, of which 2 were adults. In all the cases the bone-marrow was very cellular. Giant cells and nucleated erythrocytes were seen and eosinophile cells were found in abundance. Lymphoid cells and neutrophilic leukocytes were present in fair numbers. The principal cells, however, seen in all cases were about the size of and closely resembled the plasma cell. They formed the bulk of the cells found in the bone-marrow.

Roger[2] found the bone-marrow absolutely normal in one case, and in another evidence of slight reaction of the medullary tissue.

Heart.—The cardiac muscle suffers in scarlet fever from two chief causes—the scarlatinal poison and, secondarily, from involvement of the kidneys. The most common changes observed are cloudy swelling and fatty degeneration, processes are observed in many infectious diseases.

Romberg[3] has pointed out that the interstitial connective tissue, as well as the myocardial tissue, shows pathological alteration. The muscle fibers are separated by masses of cells and the arterial blood-vessels exhibit distinct inflammatory changes.

Pearce, in an examination of 9 cases, demonstrated fatty degeneration in 5. Segmentation and fragmentation of the myocardium were observed in a few instances.

The above changes doubtless result from the poison of the disease. The heart frequently undergoes hypertrophy and dilatation as a result of a coexisting nephritis.

Friedländer[4] states that in children with nephritis the heart increases in weight on an average about 40 per cent. Jäger is of the opinion that two-thirds of all cases of scarlatinal nephritis are accompanied by cardiac *hypertrophy* and often by *dilatation*. When the integrity of the heart muscle is compromised in the earlier days of the disease by the fever and the scarlatinal poison it becomes unable to withstand the increased pressure later when the kidneys become involved, and thus undergoes dilatation. Silberman[5] explains the heart changes as follows: (1) There is no disease in which the elimination of water is so suddenly and enormously diminished as in scarlatinal nephritis; (2) the glomeruli are principally affected; (3) there is extensive involvement of the kidney structure; (4) the edema compresses the blood-vessels of the skin and in this way increases heart-pressure; (5) increased resistance in the aortic system is more readily followed by cardiac hypertrophy in children than in adults.

[1] Loc. cit. [2] Loc. cit.

[3] Ueber die Erkrankungen des Herzmuskels bei Typhus abdom., Scharlach und Diphtheria, Deutsch. Arch. f. klin. Med., vols. **48** and **49**.

[4] Ueber Herzhypertrophie, Du Bois-Reymond, Arch. f. Physiol., 1891.

[5] Jahrbuch f. Kinderh., 1894, vol. **37**. Quoted by Forchheimer: Loc. cit.

Riegel[1] states that increased arterial tension accompanies all cases of scarlatinal nephritis, and as a result thereof *hypertrophy* of the heart takes place. The enlargement is sometimes observed a few days after the development of the nephritis. Forchheimer believes that from the effects of the scarlatinal toxin dilatation commonly takes place, even if lasting only a short time, with hypertrophy following as compensatory.

A clinically demonstrable *pericarditis* is distinctly uncommon in scarlet fever. Slight grades of pericardial inflammation are occasionally seen at autopsy. When nephritis is present effusion of serum often occurs, in some cases giving rise to enormous distention of the pericardial sac. When inflammation is present the exudate may be serofibrinous or purulent; in the latter event streptococci and staphylococci are usually found upon culture.

Endocarditis.—Endocarditis of the cardiac wall is said by von Jürgensen,[2] to be more common than valvular endocarditis. Forchheimer considers endocarditis as a very common complication of scarlet fever. The margins of the valvular segments are, in mild cases, the seat of small excrescences, in severe cases larger ones constituting a verrucous endocarditis.

Roger in 2213 personal examinations, of which 1727 were in adults, observed endocarditis but twice, while extracardiac murmurs were found 692 times. In one of the cases of endocarditis there were ulcerovegetating lesions and an abscess of the myocardium. The streptococcus was found to be the cause of the abscess.

Antra of Highmore.—Pearce found an inflammation of these cavities in 3 cases. In 2 both cavities were filled with an abundant purulent fluid, and the process was a true empyema. In both of these cases both middle ears were infected, and in one of them the sphenoidal sinus was filled with a greenish-yellow pus.

Pulmonary Complication.—In a series of 23 autopsies Pearce found *bronchopneumonia* in 8 cases, usually in the form of small, discrete nodules, scattered along the back or base of the lung. In 2 cases the process was confluent, involving the greater portion of one or more lobules. In 5 of these cases both the Streptococcus and the Staphylococcus aureus were found. In 1 case the latter was found associated with the pneumococcus; in 1 case the streptococcus was found alone.

A serofibrinous pleurisy was noted in 1 case as the result of streptococcus infection, and in another an empyema with atelectasis of the lung. In the latter a small abscess cavity was found on the surface of the lung.

Kidneys.—A voluminous and somewhat confusing literature has accumulated upon the subject of scarlatinal nephritis.

Klebs, in 1876, was one of the earliest writers to call attention to a glomerulo-nephritis occurring during convalescence from scarlet fever.

[1] Ueber die Veränderungen des Herzens und des Gefässystems bei Acuter Nephritis, Ztschr. f. klin. Med., 1884, vol. 7.

[2] Loc. cit.

He divided the kidney alterations into three groups: (1) A granular desquamation of the epithelium in the febrile stage; (2) an interstitial nephritis frequently seen late in the disease; the kidney in this condition is large, lax, smooth on section and shows grayish-white nodules; (3) a glomerulo-nephritis during convalescence.

In 1883 Friedländer, from a careful study of the kidneys in 229 autopsies, divided scarlatinal nephritis into three classes: (1) An early catarrhal nephritis, occurring during the first week; (2) an interstitial nephritis in which the kidney is large, white and hemorrhagic; this form occurs in severe cases with bad throats and other septic complications; (3) an acute glomerulo-nephritis which develops during convalescence. The latter condition occurred in 42 cases and was regarded by Friedländer as the most characteristic kidney lesion of scarlet fever. In this condition the interstitial tissue is practically normal, the glomeruli being solely involved.

Councilman, in 1897, characterized the condition of the kidneys in 3 cases of scarlet fever as a pure interstitial nephritis. He states that glomerular nephritis occurs chiefly in measles, acute endocarditis and diphtheria, and acute non-suppurative interstitial nephritis in diphtheria and scarlet fever. In the latter disease the kidney is large, pale and mottled. The principal lesion is an acute cellular infiltration with a few phagocytic endothelial cells and leukocytes. The origin of the plasma cells is presumed to be lymphoid cells which have undergone conversion in the spleen, and which emigrate from the bloodvessels and undergo mitotic change in the kidneys.

Pearce,[1] in a study of 23 cases, found degenerative changes in all. Of 8 specimens examined in the fresh state, 6 showed a more or less marked fatty degeneration. *Acute interstitial nephritis* was the most important lesion present. In 4 cases this process was extensive and in 5 slight. In the former the cellular infiltration was most marked in the cortex just beneath the capsule, around the glomeruli and around the bloodvessels in the intermediate zone. The cellular areas were made chiefly of plasma cells with a few lymphoid cells and leukocytes. *The glomeruli were unaffected.* These cases were fatal on the eighth, ninth, fourteenth and fifteenth days respectively.

From the writings of various authors it is seen that a considerable difference of opinion exists as to the most characteristic kidney changes in scarlet fever. Councilman expresses the view that differences in local resistance doubtless influence the susceptibility of the various structures. He believes that in all serious lesions of the kidneys the changes in some cases may be principally in the glomeruli and in others in the interstitial connective tissue. The glomerular lesions may be accompanied by degenerative alterations in the epithelium of the tubules, which may or may not be secondary. Hyperplasia of the connective tissue cannot be regarded as secondary to tubular changes. Certain investigators, particularly Marie, Haskine, Guinon and Babes have found streptococci in nearly all forms of scarlatinal nephritis.

[1] Loc. cit.

CHAPTER VIII.

THE DIAGNOSIS, PROGNOSIS, SERUM PROPHYLAXIS AND TREATMENT OF SCARLET FEVER.

THE DIAGNOSIS OF SCARLET FEVER.

When scarlet fever exhibits itself in a pronounced and typical form the diagnosis is very simple. As is the case with all diseases, however, aberrant and unusual cases quite frequently present themselves, in which circumstance the establishing of the nature of the disease offers the most perplexing difficulties.

We are of the belief that more errors of diagnosis are made in connection with scarlet fever than with any other acute infectious disease. On the one hand, many cases of extremely mild scarlet fever are overlooked and, on the other hand, rashes from other causes resembling that of scarlatina are not infrequently diagnosed as the latter disease.

It should be remembered that there is no one symptom of scarlatina which is pathognomonic of the disease. The rash, the most conspicuous symptom, and the one which has given the affection its name, is not in itself characteristic, inasmuch as an almost identical exanthem may occur in other conditions. Nor does its absence entirely exclude the diagnosis of scarlet fever. Indeed, we may have a scarlet fever without eruption, *scarlatina sine eruptione;* without fever, *scarlatina sine febre;* or without sore throat, *scarlatina sine angina.*

When all of the symptoms of scarlet fever are developed an unmistakable syndrome is presented. Who could fail to diagnose a disease characterized by sudden vomiting, high fever, prostration, diffuse punctiform rash, circumoral pallor, red and swollen throat, enlarged glands, strawberry tongue, followed by desquamation and albuminuria? But, unfortunately, this picture is often incomplete. Those who have had experience with scarlet fever have observed that in severe cases the various symptoms are usually well pronounced, whereas in mild cases all of the symptoms are commonly poorly marked. When the eruption is intense the throat is usually severely attacked, the tongue is characteristic and the fever is high. When, on the other hand, the general symptoms are very mild the rash is, as a rule, faint or poorly developed. It is under the latter circumstances that the diagnosis becomes so difficult, for the complex of symptoms upon which the foundation of the diagnosis rests is too weak to support it.

How often do we see cases in which the rash is faint, the constitutional symptoms mild and the throat and tongue uncharacteristic! The evidence appears very slender upon which to base the diagnosis

of a disease which necessitates two or more months of isolation. Under these circumstances the physician will do best to postpone the pronouncement of a diagnosis until the further course of the disease is watched. *In some cases it remains impossible to be sure of the scarlatinous nature of the disease.*

Specific Diagnosis.—The Dick skin test is invariably positive during the *first two or three days* of scarlet fever, and since the interpretation is made twenty to twenty-four hours after the injection of toxin, is sometimes of value in the diagnosis of the disease. A *positive reaction* indicates that the person is susceptible and may have scarlet fever; *a negative reaction, however, is of greater diagnostic value, since it indicates that the individual is immune and that the rash is not scarlatinal,* although it does not exclude the possibility of the presence of Streptococcus scarlatinæ in the fauces. Zoeller[1] states that a positive Dick reaction in scarlet fever is sometimes followed two or three days later by blanching of the area due to the local production of antitoxin and calls this the toxin-extinction reaction.

Cultures of the naso-pharynx for Streptococcus scarlatinæ are sometimes of value. These should be made on blood-agar plates and the hemolytic streptococci studied. Streptococcus scarlatinæ may be differentiated from other hemolytic streptococci by the rapid opsonic method of Tunnicliff,[2] the agglutination test of Stevens and Dochez[3] or by the toxin neutralization test of the Dicks.[4] The first two conducted with concentrated convalescent or antiscarlet-fever serum are particularly satisfactory methods for the average laboratory.

Rosenow[5] has described a method of rapid diagnosis consisting of removing mucus and exudate from the throat into saline solution, centrifuging and using the clear fluid in a precipitin test with antiscarlet-fever antitoxin. It would appear to be worthy of trial, since 91 per cent of scarlet-fever cases are said to have yielded positive reactions, although from 2 to 6 per cent of control cases, including follicular tonsillitis also yielded positive reactions.

A blood examination is also of some value, since an increase of the total leukocytes with an increased percentage of the polymorphonuclear neutrophiles and *eosinophiles* are rather constant changes in scarlet fever.

Diagnosis by the Schultz-Charlton Serum Extinction Reaction.—Schultz and Charlton,[6] in 1918, observed that when 1 cc. of serum from a normal person or from one convalescent from scarlet fever was injected into the skin of a patient with acute scarlet fever, a blanching of the skin at the site of injection occurred. On the contrary, no blanching followed the injection of serum from persons with acute scarlet fever. Similar results were subsequently obtained by other observers. They concluded that the test had no diagnostic value, and that absence of

[1] Compt. rend Soc. de biol., 1925, **92**, 337.
[2] Jour. Am. Med. Assn., 1927, **87**, 625.
[3] Ibid., 1926, **86**, 1110.
[4] Ibid., 1925, **84**, 802.
[5] Ibid., 1926, **86**, 9.
[6] Ztschr. f. Kinderh., 1918, **17**, 328.

blanching gave no help in the diagnosis of scarlet fever in the person from whom the serum was obtained, because at times normal serum did not occasion blanching.

A study by Mair[1] suggested, however, that the test nevertheless may have distinct value in the diagnosis of scarlet fever. Briefly, Mair's observations showed that a local disappearance or blanching of the scarlet-fever rash follows the intracutaneous injections of the serum of persons convalescent from scarlet fever and of most normal persons. The serum of some normal persons, however, failed to cause blanching. Mair explained the sequence of events in the following way: In scarlet fever a toxin is elaborated to which are due the clinical manifestations of the disease, including the eruption on the skin. Recovery follows the production of antitoxin. If the serum of a person convalescent from scarlet fever is injected into the skin of a patient in the acute stage of the disease, the antitoxin in the serum neutralizes the local toxin and, the cause of the eruption being removed, blanching follows. If, however, the serum of a person in the acute stage of the disease is injected there is no blanching, as the serum contains no antitoxin. The serum of normal persons also often causes blanching, but to this there are exceptions, especially in children of the age when scarlet fever most often occurs. Mair believes that those normal persons whose serum causes blanching have antitoxins in their blood, *i. e.*, these persons are immune from previous attacks of scarlet fever which often may have been mild and even unrecognized, while those whose serum does not cause blanching are susceptible to the disease.

Birkhaug[2] found that the serum from normal persons, without history of scarlet fever or general septic infections, produced the extinction phenomenon in 4 of 6 cases on the second day of the rash and in 1 of 7 cases tested on the third day of the rash. Serum from convalescent scarlet-fever patients produced it in 24 of 27 cases tested, or 89 per cent, during the first sixty hours of the rash, but did not cause blanching seventy hours after the appearance of the rash. Dochez's serum produced it in 40 cases, or 100 per cent, during the first sixty hours of the rash. It continued to produce blanching seventy hours after the appearance of the rash, but did not blanch eight days after the appearance of the rash. This indicates that the Dochez serum possesses the same specific property that is found in normal and convalescent serum but contains this specific property in considerably greater concentration. Blood serum from scarlet-fever patients first showed the property of producing the phenomenon about the eighth day of the disease. Epinephrine, normal horse serum and diphtheria antitoxin failed consistently to produce the phenomenon in scarlet fever. Normal human serum, convalescent scarlet-fever serum and Dochez's serum failed consistently to produce blanching reactions in

[1] Lancet, 1923, ii, 1390.
[2] Jour. Clin. Invest., 1925, 1, 273.

other eruptive diseases. Rash extinction areas were directly proportional in size to the amount of serum injected.

Toomey and Nourse[1] have found that if two convalescent serums are used which produce definite blanching in a given case they will complement each other and give 100 per cent reactions in scarlet fever. Levin and Parsons[2] and Lees[3] have also reported favorably upon the diagnostic value of this serum-extinction phenomenon.

In *conducting the test* at least 0.2 to 0.5 cc. of antiscarlet-fever antitoxin or potent convalescent serum is injected *intracutaneously* into a patch of erythema within forty-eight hours after its appearance; a sharp stinging pain is felt and, of course, the serum must be sterile.

There is an immediate raised pale area the result of the intracutaneous injection surrounded by a deeper erythema but these subside with an hour or two followed in eighteen to twenty-four hours by a small central area of erythema due to trauma surrounded by a distinct irregular area of blanching varying from 1 to 2 inches or more in size, which may become more marked on the second day and persist until all rash has disappeared. This constitutes a *positive reaction* due to the local neutralization of the toxin held responsible for the capillary changes of the scarlet-fever rash and the test is of value as an aid in diagnosis when conducted within the first forty-eight to sixty hours after the appearance of the rash.

Etiological Evidence.—The diagnosis in cases of scarlet fever with obscure symptoms is often simplified by the discovery of the disease in a person to whom the patient has been exposed. In institutions for children the existence of an epidemic often clarifies an individual diagnosis which would be quite impossible to make under other circumstances. Close inquiry and examination will sometimes discover a desquamating and hitherto unrecognized case of scarlet fever to be the origin of an institution epidemic.

The diagnosis of scarlet fever in doubtful cases is sometimes confirmed by the disease being transmitted by the suspected patient to another person.

Diagnostic Value of the So-called Strawberry Tongue.—In the very beginning the tongue in scarlet fever is heavily coated with a whitish fur, through which scattered red papillæ are frequently visible. In about forty-eight hours the coating peels off and there is seen a red tongue studded with enlarged papillæ. This condition of the tongue is certainly a symptom of considerable diagnostic importance, and its presence or absence in doubtful cases should be determined and considered in formulating the diagnosis. But several sources of error must be kept in view. In mild cases of scarlet fever in which the rash and general symptoms leave doubt as to the nature of the disease the tongue often fails to present its characteristic appearance. We cannot agree with McCollom, of Boston, who says that the enlargement of

[1] Am. Jour. Dis. Child., 1924, **27**, 95.
[2] Ibid., 1925, **30**, 232.
[3] Jour. Am. Med. Assn., 1927, **88**, 1133.

the papillæ is present in every case of scarlet fever, if carefully looked for. We have certainly seen a number of children in scarlet-fever wards whose tongues have been quite normal in appearance. Most of these children had mild attacks.

On the other hand, the tongue in well persons shows a variable amount of prominence of the lingual papillæ. We have examined the tongues of a large number of people with a view of determining this point. Anyone who repeats this experience may satisfy himself that the tongue under normal conditions exhibits wide variations in the size and prominence of the papillæ. Moreover, there are certain chronic forms of superficial glossitis in which the papillæ are quite large.

It must be remembered, too, that the most typical strawberry tongue may, in rare cases, occur in affections other than scarlet fever. In a few severe cases of scarlatiniform erythema, occurring during the course of smallpox, we noted very distinct "strawberry" tongues.

However, these exceptions do not invalidate the force of the statement that the presence of pronounced enlargement of the lingual papillæ in cases suspected of being scarlet fever is strong confirmatory evidence. The negative value of the absence of the characteristic tongue is of less importance.

The Diagnostic Value of Desquamation.—The statement is sometimes made that the occurrence of desquamation after a scarlatiniform eruption proves the scarlatinal nature of the preceding exanthem. Those who have observed cases of scarlatiniform erythema of the desquamative type recognize the fact that exfoliation of the epidermis is not a phenomenon peculiar to scarlet fever (Figs. 103 and 104).

It is a mistake to regard every diffuse rash that desquamates as scarlet fever. The eruption of scarlet fever is, in all probability, of toxic origin; there are other toxins which appear to be capable of exciting rashes which resemble that of scarlatina. Scaling is the terminal stage of certain pathological alterations in the skin, and the changes in the skin in scarlatiniform erythema are much the same as those occurring in scarlet fever.

The scaling in certain cases of desquamative scarlatiniform erythema is much more extensive than occurs ordinarily in scarlet fever. The occurrence of well-marked lamellar desquamation has more significance, therefore, in differentiating scarlet fever from other affections than from these exfoliating erythemata.

It may be true that the amount of scaling in a rash of given intensity is more pronounced in scarlet fever than in most rashes which simulate it; but exception must be made of desquamative scarlatiniform erythema, which not infrequently causes an exfoliation of the skin in large areas, leading, upon the palms and soles, to the throwing off of the epidermis *en masse*. This occurs in comparatively few cases in scarlet fever.

Too much importance has been attached to the mere occurrence of

desquamation in scarlet fever; the time of the onset of scaling, its mode of progression and its persistence are of more diagnostic importance.

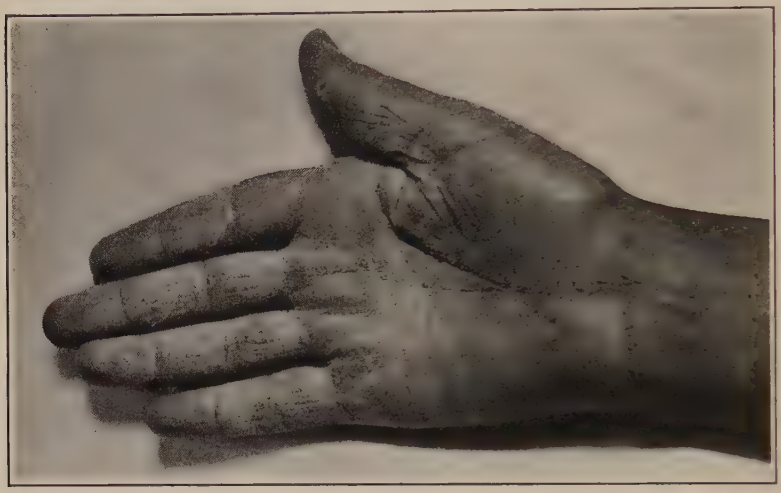


FIG. 103.—Desquamation indistinguishable from that of scarlatina, following a scarlatinoid erythema occurring during the course of smallpox.

FIG. 104.—Desquamation in a *recurrent scarlatinoid erythema* closely resembling that of scarlet fever. This patient has had two attacks almost every year for twenty-nine years.

Desquamation in scarlet fever is usually observed first upon the face; this is often seen from the fourth to the sixth day; about the sixth day

the same process is noted upon the neck and upper portion of the chest. The hands ordinarily begin to desquamate from the twelfth to the fourteenth day. Upon the feet scaling may not commence until the third week.

Scarlatinoid eruptions, in our experience, begin to scale more quickly, particularly upon the hands and feet. We have seen a well-marked scarlatiniform eruption occurring in smallpox lead to exfoliation of large pieces of the palmar and plantar epidermis on the sixth day. We believe, also, that scarlet-fever scaling persists longer than the scaling after scarlatinoid rashes. We should not insist upon the correctness of this observation, however, as scarlet-fever patients are scrutinized more closely and for a longer period than the non-scarlatinal cases; minute desquamation would thus be detected for a long time in scarlet fever and overlooked, perhaps, in other conditions.

A form of scaling which is commonly seen in scarlet fever is that which begins just beneath the free border of the finger-nails, extending thence down the fingers and exposing to view the new pink epidermis beneath. This appearance is so frequently present as to be suggestive of the disease.

Among the affections which are to be distinguished from scarlet fever the most important are those grouped under the designation of *erythema scarlatiniforme or scarlatinoides.*

This affection, if it may be called such, is characterized by an eruption which may be quite indistinguishable from that of true scarlet fever. It may be diffused over the entire cutaneous surface and may be punctiform. It is often sudden in its onset and may be attended with malaise and moderate rise of temperature (100° to 102° F.). Occasionally the initial pyrexia is higher, but under such circumstances it soon declines. The throat may be reddened, but there is no swelling of the tonsils and usually no complaint of sore throat.

The eruption has about the same duration as that of scarlet fever, although it is often briefer. It is followed by a desquamation which is ordinarily branny, but which may take place in large flakes.

Desquamative scarlatiniform erythema, termed by some writers *acute exfoliative dermatitis*, differs from the above type in degree rather than in kind.

It is characterized by the appearance of an extensive, often punctiform erythema, which rapidly covers the entire body and is accompanied by more or less febrile disturbance. In the course of three or four days the skin begins to desquamate profusely, being thrown off in large lamellæ or sheets. Epidermal casts of the palms and soles, looking not unlike gloves or slippers, may be exfoliated. The nails may be lost and, in severe cases, the hair also. Before the skin has returned to its normal condition a relapse may occur characterized by fever, erythema and a second desquamation. In some cases three or four such relapses may take place.

This type of the disease is peculiarly prone to *recurrences*, which may

appear every six months or a year. Sometimes marked periodicity is exhibited, the recurrent attacks developing with almost calendar precision. Doubtless many of the cases of scarlet fever recorded in the literature of the subject which are alleged to have recurred five, six or more times were in reality cases of scarlatiniform erythema of the desquamative type.

These eruptions are due to toxic or septic states or to the action of drugs or sera. Simple scarlatiniform erythema may occur during the course of various infectious processes, such as rheumatism, septicemia (puerperal or other forms), pyemia, malaria, typhoid fever, etc. An evanescent scarlatiniform rash may appear before the true exanthem of measles, varicella, smallpox and vaccinia.

All grades of scarlatiniform erythema may develop during the stage of decrustation of smallpox.

Diphtheria antitoxin and other sera may produce scarlatiniform rashes. Antitoxin rashes developing in the course of diphtheria may, in some cases, so closely simulate the eruption of scarlet fever as to defy all efforts at satisfactory differentiation. Northrup[1] very truly says: "Antitoxin rashes are at times most difficult to differentiate from scarlet-fever rashes.

"At the Willard Parker Hospital in New York, where both diphtheria and scarlet fever are cared for, it has been almost beyond the power of experts to pronounce definitely upon certain cases."

Intestinal auto-intoxication may give rise to a scarlatiniform eruption. Crocker says this may follow the use of enemata, which sometimes facilitate the solution and absorption of toxins.

The drugs which most commonly give rise to scarlatiniform eruptions are quinine, mercury, belladonna, salicylic acid, antipyrine, acetanilide, and the entire barbituric acid series, including veronal, luminal, etc. Many other medicaments occasionally produce scarlatinoid rashes in susceptible subjects. The eruption resulting from the administration of quinine is one of the most frequent and the most likely to be confounded with scarlet fever. It may be followed by well-marked desquamation.

It is often a matter of great difficulty to differentiate scarlatiniform erythema from true scarlet fever. In the former the invasive symptoms are often extremely mild; the patient commonly does not complain of feeling ill; the temperature elevation is slight, perhaps 101° or 102° F. The throat may be reddened, but the tonsils and uvula are not swollen and exudate is not present upon the tonsils.

The reddened, papillated tongue is, as a rule, absent. The eruption may begin upon any portion of the body; it may be patchy and irregular, or it may be diffuse, with or without punctation. The glands at the angles of the jaws are not apt to exhibit any pronounced enlargement; albuminuria is rare and otitis media does not occur.

[1] Addenda to von Jürgensen's article on Scarlet Fever, Nothnagel's Encyclopedia of Practical Medicine, American edition.

It is thus seen that scarlatiniform erythema may be readily distinguished from a well-pronounced attack of scarlet fever; but the fact must not be overlooked that there are many mild cases of scarlet fever in which the fever is slight, the eruption poorly marked and the other symptoms correspondingly uncharacteristic.

The significant feature in scarlatiniform erythema, particularly when the rash is well pronounced, is that *the intensity of the eruption is out of all proportion to the amount of constitutional disturbance.* There is not present the prostration and high fever which would accompany a rash of similar severity in scarlet fever. Furthermore, there is rarely seen in scarlatiniform erythema a severe sore throat.

Another point of great diagnostic importance is the history as to previous attacks; the tendency to recurrence is a well-registered feature of scarlatiniform erythema.

We have occasionally had patients sent into the Philadelphia Hospital for Contagious Diseases with scarlatiniform erythemata which had been diagnosed as scarlet fever. We recall a young man who presented a generalized scarlatinoid eruption of moderate intensity which inaugurated the onset of a typical intermittent fever. Another patient, a girl, aged five years, sent in from a foster home, had an eruption indistinguishable from scarlet fever, which proved to be a prodromal chickenpox eruption; this girl contracted a well-pronounced scarlet fever six days after admission to the scarlet-fever ward.

A young woman, sent into the hospital with an intense erythema which was diagnosed as scarlet fever, passed through an attack of exfoliative dermatitis, with profuse desquamation and subsequent loss of hair and nails. She had previously received large doses of antipyrine, and this drug was found in the urine.

We also had under observation a young man, aged eighteen years, who was sent into the Philadelphia Hospital for Contagious Diseases *three times within a year* with the diagnosis of scarlet fever. He was admitted to the Hospital first on June 3, 1902. He had vomiting, sore throat, slight fever and a generalized scarlatiniform eruption. He desquamated profusely. The scaling lasted almost nine weeks, and the patient was discharged on September 3, 1902.

The patient was *readmitted* on January 9, 1903. He had sore throat, headache, slight fever and a well-marked scarlatiniform rash. Slight desquamation occurred upon the face and trunk.

The patient was admitted for the third time on June 28, 1903. He had had repeated vomiting, headache, sore throat and some fever; on admission there was a generalized, well-pronounced scarlatiniform eruption, not punctated, however. The tongue was heavily coated, but after this disappeared there was no enlargement of the papillæ. Desquamation was well marked, being particularly copious on the hands and feet. The latter were still peeling in large lamellæ at the end of a month.

Each of these attacks resembled scarlet fever sufficiently to cause the resident physician to admit the patient.

We would call attention, however, to the fact that the fever and sore throat on each occasion were very slight. There was no prostration and the characteristic tongue was absent. We have no doubt that the patient was suffering from a scarlatiniform erythema, possibly due to intestinal auto-intoxication.

If eruption and desquamation occur upon the forehead and the eyelids the disorder is probably a scarlatinoid erythema and not true scarlet fever.

Drug Rashes.—Quinine, antipyrine, salicylates, veronal and its congeners, opium, belladonna, chloral and mercury at times produce eruptions which may closely simulate that of scarlet fever. The eruption resulting from quinine is the most frequent and the most likely to be confounded with scarlet fever. As a rule, in these eruptions the constitutional disturbance is disproportionately slight, and severe sore throat, swelling of the glands, strawberry tongue and middle-ear disease are absent. The eruption often fails to begin on the chest and pursue the normal progression of the scarlatinal exanthem. The occurrence of desquamation has no diagnostic value in these cases, as the drug rashes may be followed by a variable amount of epidermal exfoliation.

A differential point of importance is the blood count. In scarlet fever there is nearly always a distinct *leukocytosis*, while in drug rashes this is not ordinarily the case.

Measles.—There is no difficulty in distinguishing between measles and scarlet fever under ordinary circumstances. There are, however, irregular cases of each disease in which the elimination of the other in the diagnosis is by no means easy.

The rash in scarlet fever is now and then blotchy, especially upon the extremities; in other cases, particularly of septic scarlatina, a profuse rhinorrhea may be present, even early in the course of the disease; these symptoms, associated with an otherwise irregular symptom-complex, may produce quite a resemblance to measles.

The eruption of measles may, as a result of coalescence of the macules, closely simulate that of scarlet fever. In some epidemics the proportion of confluent measles eruptions appears to be greater than in others. Some years ago during the prevalence of a particularly severe form of measles we noted a frequent tendency of the exanthem after the lapse of twenty-four or forty-eight hours to become confluent and present the appearance of a diffuse scarlatiniform eruption. Usually, however, there may be seen somewhere on the trunk or extremities sharp margination of the eruption with contiguous areas of pale, normal skin.

In measles the face is earlier and more copiously affected than in scarlet fever; the eruption is dusky red in color, palpably raised above the skin, and distinctly blotchy; it appears later than the eruption of scarlet fever (about the fourth day); there is a prodromal stage, during which time catarrhal symptoms affecting the eyes, nose, larynx and bronchial tubes are present, producing watery eyes, sneezing, running

nose, hoarseness and frequent cough. The initial fever is not as high as in scarlatina and the tendency to vomiting is less. Sore throat, great glandular intumescence, strawberry tongue, lamellar desquamation and nephritis, commonly seen in scarlet fever, are absent in measles.

The presence of Koplik spots upon the buccal mucous membrane would decide in favor of measles.

The discovery of a marked leukocytosis would, it is claimed, point strongly toward the scarlatiniform nature of the disease.

In scarlet fever there is a definite leukocytosis; this is not true of uncomplicated measles.

At times a secondary roseolous or measles-like eruption appears later in the course of scarlet fever. This is regarded by Thomas as a pseudo-relapse, but it seems to us to be of the nature of a septic rash.

Smallpox.—Scarlet fever may be confounded with the prodromal scarlatiniform rash that is occasionally seen during the initial stage of smallpox. The absence of angina and the appearance of the variolous papules will make the diagnosis clear.

During the later pustular stage of variola an intense scarlatiniform eruption at times develops which may raise the question of a secondary infection with scarlet fever. There may be high fever, prostration and subsequent desquamation. The absence of vomiting, sore throat, the strawberry tongue and the development of the eruption about the twelfth to the fifteenth day of smallpox will usually enable one to recognize the character of the rash.

Influenza.—Influenza is sometimes accompanied by a scarlatiniform eruption which may cause scarlet fever to be suspected. The presence of severe muscular pains and catarrhal symptoms, and the absence of the angina and the characteristic tongue, together with attention to the character of the prevailing epidemic will usually suffice to distinguish the two affections.

Rubella.—With the usual type of rubella scarlet fever scarcely comes into differential conflict. It is with that form which tends to present a diffuse eruption that errors may arise. (See article on Rubella.)

Diphtheria.—Ordinarily scarlet fever and diphtheria have but little in common, and yet errors in diagnosis are not infrequent. Too often physicians glance into the throat, see exudate present upon the tonsils, and perhaps upon the soft palate, and straightway make the diagnosis of diphtheria. Time and time again have we received calls at the Philadelphia Hospital for Contagious Diseases for cases of diphtheria, only to discover on seeing the patient the presence of a scarlatinal rash. Diphtheria is ordinarily not accompanied by an exanthem.

Vomiting is much more common as an invasive symptom of scarlet fever than of diphtheria. The exudate in diphtheria is tough and thick, of a grayish or grayish-yellow color, and quite firmly adherent to the underlying mucous membrane. That of scarlet fever is yellowish, thin and smeary, and more easily wiped off. In scarlet fever, moreover, the throat ordinarily shows more intense redness and

edema than in diphtheria. The soft palate commonly presents a punctated, reddened appearance.

Enlargement of the maxillary and submaxillary glands occurs in both diseases. The temperature in diphtheria tends to subside in a few days; in scarlet fever it commonly persists for a longer period. The strawberry tongue of scarlatina is absent in diphtheria.

Otitis media may occur in both diseases, but it is more common in scarlet fever. Albuminuria is an *early* symptom in diphtheria and a *late* symptom in scarlet fever. It is present in about one-half or more of the cases of diphtheria and is commonly found on the third or fourth day. A transient albuminuria may occur early in severe cases of scarlatina accompanied by high fever, but the true scarlatinal nephritis is ordinarily discovered about the end of the third week. The early albuminuria of diphtheria is apt to be associated with the presence of tube casts.

While the finding of Klebs-Loeffler bacilli in the throat is of great diagnostic importance, their presence does not exclude scarlet fever. At the Philadelphia Hospital for Contagious Diseases Welch and Schamberg had cultures made of all scarlet-fever patients on admission to the hospital. The percentage of cases in which diphtheria bacilli were found varied from time to time. It has been as low as 8 in 100 and as high as 30 in 100. It is by no means always the bad throats that give positive cultures. In many of the cases in which the Klebs-Loeffler bacilli are found there is no exudate at all in the throat.

That diphtheria and scarlet fever may occur at the same time is generally admitted. In our experience scarlet fever has more often developed in the course of diphtheria than the reverse. Diphtheria is more apt to appear after the acute symptoms of scarlatina have subsided. Scarlet fever, on the other hand, not infrequently makes its appearance early in the course of diphtheria.

To distinguish between the scarlatiniform rash that occasionally occurs in diphtheria and a true complicating scarlet fever is a most difficult and, indeed, an often impossible task. Clinicians of experience recognize this fact. Osler, for example, says: "Scarlet fever and diphtheria may coexist, but in a case presenting widespread erythema and extensive membranous angina, with Loeffler's bacillus, it would puzzle Hippocrates to say whether the two diseases coexisted, or whether it was only an intense scarlatinal rash in diphtheria."

It has been our custom to regard as a complicating scarlet fever any well-pronounced scarlatiniform rash accompanied by distinct elevation of temperature; if vomiting occur and the lingual papillæ become enlarged the diagnosis is much clearer. We have sent all such cases to a mixed ward in which there have been undoubted cases of scarlet fever, and it has been extremely rare for any children thus transferred to contract scarlet fever. We have never seen an intense, well-pronounced scarlatiniform rash in diphtheria that we felt could be regarded as an erythema diphtheriticum.

Since the introduction of the use of diphtheria antitoxin the difficul-

ties of diagnosis have been increased, for a third possibility presents itself, namely, a scarlatiniform antitoxin rash.

The occurrence of scarlatiniform eruptions in diphtheria wards is always a source of anxiety. If the patient is allowed to remain other children may be exposed to scarlet fever; if, on the other hand, the patient is transferred to a mixed ward there is a risk of his contracting scarlet fever. It is well to have nearby a number of small rooms in which patients may be placed for a few days and watched. These cases tax the diagnostic acumen of even the most experienced physicians.

Tonsillitis.—An inflammation and enlargement of the tonsils with the development of exudate in the crypts is so often seen in scarlet fever as to constitute a part of the symptom-complex of this disease. It is recognized that scarlatina may occur without an exanthem. The determination of the scarlatinal character of a tonsillitis occurring in a person exposed to the infection of scarlet fever is a most difficult matter. If the exposure has been intimate the individual unprotected by previous attack of scarlet fever, the characteristic tongue appearance and the angina present and otitis media or nephritis develop, the existence of angina scarlatinosa would be highly probable. Follicular tonsillitis not infrequently develops in persons exposed to scarlatina who have previously had the disease. Thomas says that all such cases should be regarded with suspicion, but we would hesitate to regard them all as scarlet fever. The symptoms are identical with follicular tonsillitis occurring from other sources. We have known persons unprotected by a previous attack of scarlet fever to contract, on exposure to the disease, what appeared to be an ordinary follicular tonsillitis; although no eruption was discovered in these patients, they have at times desquamated on the feet in a quite characteristic manner. Patients with sore throats of this nature have also been known to communicate scarlet fever to others. It is often impossible to determine with positiveness whether or not cases of follicular tonsillitis resulting from exposure to scarlet fever are to be regarded as angina scarlatinosa.

Occasionally an erythema develops in the course of an ordinary follicular tonsillitis. This eruption is often partial and may appear first on any part of the body. The exclusion of the diagnosis of scarlatina is only possible after a careful study of all of the symptoms, general and local, and attention to the circumstances of exposure and epidemic influence. In all difficult cases a white-cell count and the "serum extinction" test may be of value.

Patients with tonsillitis should not be given salicylates, quinine, veronal or other potential erythemogenic drugs, else the diagnosis may be embarrassingly complicated.

THE PROGNOSIS OF SCARLET FEVER.

The most important factor bearing upon the prognosis of scarlatina is the character of the prevailing epidemic. Some outbreaks of scar-

let fever are of extreme mildness and others are frightfully severe. Sydenham never saw a severe case of the disease, and, therefore, spoke of it " with a sort of contempt which he was far from having for measles or smallpox." According to Trousseau, his illustrious master, Bretonneau, had not seen a fatal case of scarlet fever from 1799 to 1822; he was, therefore, satisfied that "scarlet fever was the mildest of all the exanthemata." Later experience with a severe form of the disease caused him to change his opinion and regard the malady as equally mortal with plague, typhus and cholera.

The character of scarlet-fever epidemics, as regards benignancy or severity, commonly persists for a period of years before a change in type occurs. Graves[1] has pointed out that a very fatal epidemic ravaged Ireland in 1800 to 1804. Then the type changed, and from 1804 to 1831 the affection was so wonderfully mild that scarcely any deaths occurred. In 1831, however, a malignant epidemic broke out and in a few years spread throughout Ireland, causing tremendous loss of life.

It is evident, therefore, that the mortality from scarlatina has an extremely wide range. It may fall below 3 per cent, or reach the frightful figure of 40 per cent. Johannsen states that in an epidemic in certain localities in Norway the death-rate actually reached 90 per cent; this murderous outbreak is absolutely without precedent.

Hirsch and Thomas hold that the average mortality of scarlet fever is about 10 per cent; the more that the death-rate exceeds this figure, the greater is the severity of the epidemic. When the death-rate remains below 10 per cent the epidemic may be looked upon as mild. Thomas, in enumerating the most fatal epidemics of scarlet fever, says Hambursin in Namur lost about 30 per cent; Arrigoni, about 40 per cent; Salzmann, in Esslinger, from 1853 to 1857, about 36 per cent; at Hornbach, in the Palatinate, in 1868 to 1869, 34 per cent.

The severity of scarlet fever has been diminishing within recent years. Johannsen says that among 84,580 reported cases in Norway there were 12,789 deaths, a mortality of 14.17 per cent. He regards the normal mortality in Norway as 13 per cent.

Caiger[2] states that during twenty-three years 81,350 cases of scarlet fever were treated in the hospitals of the Metropolitan Asylums Board of London, with a combined mortality of 8 per cent. Since 1874 the annual percentage has progressively fallen from 12.2 to 5.9.

Scarlet-fever Mortality in London Hospitals. (Caiger.)

Year.	Notifications.	Deaths.	General mortality, per cent.	Hospital mortality, per cent.
1890	15,330	876	5.71	7.86
1891	11,398	589	5.17	6.67
1892	27,095	1174	4.33	7.28
1893	36,901	1596	4.32	6.11
1894	18,440	962	5.21	5.92

[1] Quoted by Trousseau, American edition, p. 137.

[2] Loc. cit., p. 128.

The higher mortality in the hospitals is said to be due to the larger proportion of severe cases sent in.

The death-rate in the Philadelphia Hospital for Contagious Diseases has been as follows:

SCARLET-FEVER MORTALITY IN THE PHILADELPHIA HOSPITAL FOR CONTAGIOUS DISEASES.

	Cases.	Deaths.	Percentage.
1891	63	2	3.17
1892	159	14	8.80
1893	170	32	18.80
1894	129	11	8.52
1895	163	11	6.73
1896	253	18	7.11
1897	858	99	10.37
1898	380	45	11.84
1899	604	57	9.43
1900	646	53	8.20
1901	1115	108	9.68
1902	673	56	8.32
Total	5213	506	9.72

From 1902 the mortality in the Philadelphia Hospital for Contagious Diseases has progressively declined. This has been more particularly pronounced since the introduction of the use of "specific antitoxin."

In 1926 a considerable use of this serum was made and the death-rate among 2414 cases was 1.37 per cent. In 1927 there was a more extensive employment of the antitoxin with a consequent reduction of the mortality to the *marvelously low figure of* 0.68 *per cent.*

The factors that influence the prognosis in individual cases are: (1) The age of the patient; (2) the virulency of the infection; (3) the character and severity of the complications. The latter are greatly lessened by the use of specific antitoxin.

Age.—Age affects the prognosis in a most striking manner. The younger the child group, the higher the mortality.

In the cases of Welch and Schamberg in the period from 1898 to 1902, the general mortality among 5213 was 9.72 per cent; in children under five years of age it was about double this figure—18.6 per cent.

The mortality for the different age periods of patients treated in the Philadelphia Hospital for Contagious Diseases during the period referred is herewith subjoined:

	Cases.	Deaths.	Percentage.
Under 1 year	40	13	32.50
1 to 5 years	1670	305	18.32
5 to 10 "	1766	106	6.00
10 to 15 "	476	19	3.99
15 to 25 "	295	18	6.10
25 and upward	133	7	5.27

The above table shows the highest mortality under five years of age, and particularly under one year. In the first year of life about one-third of our patients died.

After the age of five years has been passed the mortality diminishes progressively. The death-rate, in our own experience, reaches its minimum in children between the ages of ten and fifteen years.

Virulency of Infection.—Virulency of infection is indicated by great severity of the invasive symptoms. The prognosis is bad when the temperature is excessively high—106° or 107° F.; when convulsions, stupor, or coma develop; when the eruption is irregular or partial in distribution or when it is livid, suppressed or hemorrhagic. These are malignant cases and the patient is, as a rule, overwhelmed early in the course of the disease.

During the first or second week the appearance of severe *anginose* or *septic* symptoms renders the diagnosis unfavorable.

Patients with a sloughy throat with tendency to gangrene, great lymphatic enlargement, purulent rhinitis and otitis are apt to succumb to the poison of the disease.

Influence of Complications.—The complications which are most apt to cause death are nephritis, purulent otitis, meningitis, endocarditis, pneumonia, etc. The symptoms of evil omen in nephritis have already been referred to. It should be remembered that cases of scarlatina that begin in the most benign manner may develop a severe nephritis with its attendant dangers. This complication comes on late, during the third week, at a period when the patient and his family have perhaps looked forward to complete convalescence.

A favorable course of the scarlet fever may be anticipated, under ordinary circumstances, when the invasive symptoms are but moderately developed, when the throat is but mildly involved, when the eruption appears at the proper time, gradually reaches its maximum and is uniformly distributed; when the fever steadily declines with the fading of the exanthem, and when complications are absent or of short duration.

In forecasting the result of an attack of scarlet fever it is wise for the physician not to give an unqualifiedly favorable prognosis, even in mild cases; the liability to serious complications in this disease should cause him to make some reservation in the expression of an opinion as to the outcome of the illness.

THE SERUM PROPHYLAXIS OF SCARLET FEVER.

Probably the first serum to be used in the treatment of scarlet fever was the antistreptococcus serum of Marmorek in the early nineties. The results, however, were not encouraging.

But in 1901 Moser[1] employed a new antistreptococcus serum prepared by the immunization of horses with streptococci of scarlet-fever origin with much better results. Of 400 cases treated with serum the mortality was 8.9 per cent as against an average mortality of 13.09

[1] Berl. klin. Wchnschr., October 20, 1902, p. 995.

per cent in other hospitals in Vienna in which serum was not used. Baginsky, using Aronson's antistreptococcus serum, had a mortality of 11.3 per cent as against 17.3 per cent treated without serum.

Unquestionably Moser's serum deserved much more attention than it received because he evidently had one comparing favorably with those prepared by Dochez and the Dicks a few years ago and which have proven very valuable additions to our methods of serum prophylaxis and treatment of the disease.

Kinds of Immune Serum.—Dochez immunized horses with Streptococcus scarlatinæ itself, and Blake, Trask and Lynch[1] and Birkhaug[2] reported very favorable results with it in the treatment of scarlet fever. Shortly thereafter the Dicks[3] announced a second serum prepared by the immunization of horses with the toxin alone. At the present time the serum is being prepared by the immunization of horses with both the toxin and organisms, and this would appear to be the correct method in order to render it antibacterial as well as antitoxic.

The serum as first prepared was used in a raw state and produced severe reactions and serum sickness in as high as 60 per cent of cases. At present antiscarlet-fever sera are being concentrated in the same manner as diphtheria and tetanus antitoxins and the incidence of serum sickness has been reduced to about 10 to 20 per cent.

Roger,[4] as early as 1896, treated a severe case of scarlet fever with a subcutaneous injection of 100 cc. of human convalescent blood, and states that he never before saw such a rapid recovery of so grave a case. This was followed by the report of Weisbecker[5] and of Hüber and Blumenthal,[6] the latter reporting on the treatment of 13 cases with convalescent serum with positive beneficial results in 3. Since then a rather large literature has accumulated upon the subject because the value of this type of serum treatment became well established, although interest in it has lagged since the introduction of the more potent immune sera of Dochez and the Dicks.

Standardization of Serum.—Unfortunately antiscarlet-fever serum cannot be standardized in the guinea-pig, mouse or other of the lower animals as diphtheria and tetanus antitoxins are tested because the lower animals are not sufficiently sensitive to the toxin of Streptococcus scarlatinæ. Susceptible human beings must be employed, since attempts to standardize by agglutination, opsonic and complement-fixation tests have proven inadequate. Perhaps the Ramon flocculation test may prove of value, as suggested by Dyer,[7] but this has not yet been established. The subject is further complicated by the observations of Park and Spiegel,[8] who noticed that an amount of horse antitoxic serum which would neutralize the toxin in a majority

[1] Jour. Am. Med. Assn., 1924, **82**, 712.
[2] Bull. Johns Hopkins Hosp., 1924, **36**, 1246.
[3] Jour. Am. Med. Assn., 1924, **82**, 1246.
[4] Presse méd., 1896, **4**, 245.
[5] Berl. klin. Wchnschr., 1897, **34**, 671.
[6] Ztschr. f. klin. Med., 1897, **32**, 188.
[7] Pub. Health Repts., 1925, **40**, 865.
[8] Jour. Immunol., 1925, **10**, 829.

of children would totally fail in others. It was also observed that the antitoxic serum of different horses would occasionally vary in the ability to neutralize a toxin in the same child and finally that in some individuals in whom the ordinary amount of antitoxin was not effective there was an increased amount of antitoxin.

These observations seem to prove that the scarlet-fever toxic filtrate produced by a single strain was not a single toxin, but a group of toxins, and that a person might be immune to one or more of the component toxins of a toxic broth and yet susceptible to others. They also prove that certain horses react in producing antitoxin more to one of the components and certain horses to another in much the same way as Park has shown—that of two horses receiving simultaneously the same quantity of tetanus and diphtheria toxins one may develop a potent diphtheria antitoxin and a weak tetanus antitoxin while the other will do the opposite. The same difference is noted in different animals receiving the same dose of bacterial antigen.

At the present time all antiscarlet-fever sera prepared by the large laboratories are subjected to control tests by the Hygienic Laboratory of the United States Public Health Service in Washington. In general terms, the *unit of serum is the smallest amount capable of neutralizing 50 skin-test doses of toxin* or, as stated by the Hygienic Laboratory: "The unit for measuring the strength of scarlet-fever streptococcus antitoxin is defined as the neutralizing power possessed by a definite quantity of antistreptococcic serum preserved at the Hygienic Laboratory of the United States Public Health Service under special conditions to prevent deterioration. This quantity is now equivalent to ten times the amount of scarlet-fever streptococcus antitoxin necessary to neutralize 1 test dose of scarlet-fever streptococcus toxin, each test dose containing five times the amount of scarlet-fever streptococcus toxin necessry to give in the majority of non-immune individuals in twenty-four hours following intracutaneous injection, a skin reaction 1 cm. or more in diameter."

Serum Prophylaxis of Scarlet Fever.—Usually the subcutaneous or *intramuscular* injection of an adequate amount of antiscarlet-fever serum confers an immediate immunity lasting about three weeks; unfortunately it is not always effective, and the frequent occurrence of serum sickness is objectionable. Within an hour or two after injection enough antitoxin is generally absorbed to give negative Dick skin-tests. Graham[1] observed that all of 24 cases immunized on the day of exposure escaped the disease, although 2 of 3 cases immunized two days after exposure developed it. Cushing and Longpre[2] state that in a Canadian hospital the incidence of scarlet fever among nurses was 15 per cent, whereas after immunization with serum was practised the incidence dropped to 9 per cent. Lees[3] has likewise

[1] Jour. Am. Med. Assn., 1925, **85**, 95.
[2] Union méd. d. Canada, 1926, **55**, 1.
[3] Jour. Am. Med. Assn., 1927, **88**, 1133.

rendered a favorable report, and Woody[1] believes that passive immunization should be endorsed as an emergency prophylactic measure in families and more particularly in hospitals and other institutions where scarlet fever may develop. In the Philadelphia Hospital for Contagious Diseases he has given the serum in one injection within forty-eight hours after exposure. The dosage used was as follows: In children up to three years of age (inclusive) serum to neutralize 50,000 skin-test doses of toxin was given; from the fourth to the sixth year (inclusive), 75,000 skin-test doses; to all over six years, 100,000 skin-test doses. All the cases gave a negative Dick test when retested seventy-two hours later and not one of the series developed scarlet fever during an average of from four to sixteen days' subsequent stay in the hospital. In more than 75 cases exposed to scarlet fever (through having been sent in under mistaken diagnosis of scarlet fever) but with negative scarlet-fever histories, antitoxin to neutralize 100,000 or more skin-test doses was given. The cases all had direct and most intimate exposure to scarlet fever in the ambulance, or in the wards with active scarlet-fever cases, varying in time from five to sixteen days, and not one of them developed the disease.

The subcutaneous or intramuscular injection of antiscarlet-fever serum frequently produces rather severe "kicks" or reactions, so that many physicians believe it better practice to take a chance on contracting the disease. But the incidence and severity of these has been greatly decreased of late by the use of concentrated and more "ripened" sera.

The injection of 10 to 15 cc. of human convalescent serum is also capable of immunizing against the disease and produces no "kick" or reaction, although the effects are less certain. The serum should be obtained from recent convalescents, cultured for sterility and preserved with 0.5 per cent phenol. Skrotzky and Bardakh[2] have recently reported very favorable results, but owing to the difficulty of securing the serum under proper conditions the method has not been widely employed.

THE SERUM TREATMENT OF SCARLET FEVER.

The use of antiscarlet-fever serum in the treatment of the disease has proven almost as effective as the use of antitoxin in the treatment of diphtheria.

In the Philadelphia Hospital for Contagious Diseases the mortality during the past year has been but 0.68 per cent among serum-treated cases and Dr. S. S. Woody, medical director, states that: "By its use we were able to obtain a more rapid subsidence of toxemia, more rapid fading of the rash, more prompt return to normal of the mucous membranes, a reduction in the incidence of carriers and a softening of the menace of return cases. We have given the serum intramuscu-

[1] Bull. Philadelphia Dept. Pub. Health, 1926, ii, 20.
[2] Prophylaktitchesk. Med., 1925, **4**, 28.

larly in doses equivalent of 250,000 to 700,000 skin-test doses, the size of the dose being regulated by the age of the patient, the degree of toxemia and the severity of the throat symptoms. In passing, it may be said that we have always laid great stress on the condition of the throat in estimating the severity of a given case of scarlet fever. In the use of the concentrated antitoxin now available the question of serum sickness is not a serious one. In about 100 cases receiving 30 to 60 cc. of serum, a serum sickness incidence of 11 per cent has been noted. The reactions are a little severer than those obtained from diphtheria antitoxin, but no immediate serum reactions have occurred nor have any serious symptoms been noted."

Blake and Trask,[1] Thenebe,[2] Park,[3] Dick and Dick,[4] Robb,[5] Musser,[6] Gordon[7] and others have reported favorably upon the use of the serum in the treatment of scarlet fever.

It is especially indicated in the moderately severe and septic or anginose forms of the disease. *It should be given as early as possible* and an effective dose is usually followed within twenty-four hours by a reduction in temperature and pulse-rate, a fading of the rash, an improvement of the throat, cessation of vomiting and clearing of the mind. Sometimes fading of the rash first begins and is most marked at the site of injection. In late cases the serum is much less effective and has little or no influence upon suppurative adenitis, otitis media and other septic complications.

But its early administration in large doses has greatly reduced the incidence of nephritis, adenitis, otitis media and other complications as well as materially reducing the mortality. Furthermore the administration of the serum may sometimes unmask these complications already existing by combating the systemic toxemia and render their recognition and proper treatment more certain. Stevens and Dochez[8] have used the serum successfully in the treatment of cases without rashes (scarlatinæ sine eruptione).

The serum is generally administered by intramuscular injection, but in severe cases should be given intravenously. Due care against anaphylactic reactions should be exercised as explained in Chapter XV. Scarlet-fever serum as produced at present is not nearly as likely to give a "kick" or reaction as formerly, and its administration presents no more danger than diphtheria antitoxin. The *dose* should be large in order to neutralize as soon as possible all toxin with a balance in the blood to neutralize toxin as it is subsequently produced until phagocytes remove the streptococci from the throat and prevent further production. As a general rule, the therapeutic packages of serum marketed by various firms contain an appropriate dose for average cases, but the total amount of serum required for best results will be

[1] Boston Med. and Surg. Jour., 1925, **193**, 659.
[2] Ibid., **192**, 939.
[3] Jour. Am. Med. Assn., 1925, **85**, 1180.
[4] Ibid., **84**, 803.
[5] British Med. Jour., 1926, i, 11.
[6] Jour. Am. Med. Assn., 1927, **88**, 1126.
[7] Ibid., **88**, 382.
[8] Ibid., **87**, 2137.

usually equivalent to the amount required for neutralizing from 300,000 to 2,000,000 skin-test doses of toxin.

One dose is usually sufficient for moderate cases, but if the temperature is not reduced or rises after a drop or the throat continues to look badly infected, second and third doses are required at twelve- to twenty-four-hour intervals.

Possibly the serum may be omitted in the treatment of mild cases in order to avoid serum sickness and acquire the lasting immunity usually following an attack of the disease. But mild cases sometimes become severe and the administration of serum also reduces the chance of otitis media and other complications.

The effect of serum treatment upon immunity is, however, worthy of consideration. As Davies[1] has pointed out, since the serum rapidly neutralizes circulating toxin and thereby removes the stimulus which induces a permanent active immunity, it becomes possible that patients promptly cured by antitoxin may become susceptible again, after the relatively transient passive immunity conferred by the administration of antitoxic serum has terminated. A comparison has, therefore, been attempted in the New Haven Hospital between the degree of late immunity to scarlet fever developed by former patients who were treated with scarlet-fever antitoxin during the toxemic stage of the disease and those who did not receive antitoxin. So far as can be ascertained by the limited number of observations thus far made, it appears that there may be some disadvantage in the therapeutic dosage with the antitoxin in respect to the establishment of a more lasting immunity. Experience will presently show whether or not the advent of scarlet-fever antitoxin therapy will so alter the natural course of immunization to the disease as to increase the incidence of second attacks of scarlet fever in individuals treated with serum. If it is decreased, owing to the rapid neutralization of the toxin, it may develop that in some instances relapse following inadequate antitoxin therapy is the result of the early temporary neutralization of the toxin and the consequent removal of the natural stimulus to antitoxin formation. The successful momentary combating of the actual disease may thus actually decrease the security that an attack of scarlet fever almost invariably promoted in former days.

Treatment of Scarlet Fever With Human Convalescent Serum.—Serum or citrated blood from convalescents for the treatment of scarlet fever is not employed as much at present as formerly because of the better results observed with antiscarlet-fever serum and the greater ease of securing it. But there can be no doubt of the value of convalescent serum in the treatment of septic cases providing large doses are given and there is no danger of serum sickness or other forms of anaphylactic reactions.

A review of the literature up to 1923 and the technique employed

[1] Jour. Clin. Invest., 1926, **3**, 423.

are given elsewhere,[1] and more recent reports by Bode,[2] Daniel,[3] Bernbaum,[4] Debré and Paraf,[5] Langer,[6] de Rudder[7] and others testify to the practical value of this form of serum treatment. The serum must be sterile and the dose large, like 30 to 90 cc. by intramuscular injection followed by a second dose if necessary. Zingher used citrated blood in dose of 2 to 8 ounces in a series of intramuscular injections at close intervals. Of course due care must be exercised against using the blood of syphilitics or others with transmissible diseases.

In severe cases the serum or blood may be given intravenously, but the serum should not contain agglutinations for the corpuscles of the patient and if citrated blood is given the precautions should be more rigid, as it is in truth a blood transfusion. Even serum or blood from normal individuals who have not had scarlet fever may be efficacious when given intravenously, probably because of the presence of some natural antitoxin and the non-specific effects of the serum proteins.

THE GENERAL PROPHYLAXIS AND TREATMENT OF SCARLET FEVER.

General Prophylaxis.—Scarlet fever is an endemic disease in nearly all great centers of population, and the health authorities of these commonwealths require sanitary regulations for the control and prevention of the disease.

As a prerequisite to the prosecution of this work compulsory *notification* is essential. The health authorities must know when and where scarlet fever exists in order to be able to check its farther extension. It is the custom in some cities to placard domiciles in which scarlet fever exists in order to warn persons who might be otherwise disposed to enter the infected houses.

There can be no doubt that many *infectious diseases are spread* through the mingling of children in *kindergartens* and *schools*. Scarlet fever almost invariably decreases during the summer vacation when the schools are closed, and increases again when the sessions begin. Every effort should, therefore, be made by the proper authorities to prevent the infection from being transmitted in the schools.

The procedure in vogue in most large cities at the present time is as follows: The head of the school is notified by the health authorities that one of the pupils is sick with scarlet fever and that he is not to be permitted to return, save after certified examination by a medical inspector or some other duly authorized person. Other members of the same household that are in attendance at school should likewise

[1] Kolmer: Infection, Immunity and Biological Therapy, 3d ed., Philadelphia, W. B. Saunders, 1923, p. 899.
[2] Jahrb. f. Kinderh., 1925, **108**, 354.
[3] Presse méd., 1923, **31**, 336.
[4] Michigan State Med. Jour., 1922, **21**, 249.
[5] Paris méd., 1922, **12**, 418.
[6] München. med. Wchnschr., 1925, **72**, 47.
[7] Ibid., **72**, 1281.

be debarred until they have safely passed the limits of the incubation period.

A child who develops an attack of scarlet fever should be debarred from school for a period of time *not less than two months*. Where nasal or aural discharge or desquamation persists beyond this period the enforced vacation must be still further extended. While such a rule often works hardship, it will be found to best conserve the public health and welfare.

In most communities medical inspectors make frequent examinations of the pupils in the public schools, with a view to determining the existence of suspicious sore throats, late desquamation, etc. Where such medical service cannot be commanded, teachers should be instructed in the symptoms of scarlet fever, so that cases presenting suspicious symptoms might be immediately sent home. A careful and intelligent teacher may in this manner often discover the disease in its incipiency and send the patient away before infection is conveyed to others.

If these precautions be carried out it will not be found necessary except, perhaps, in extensive epidemics to close public schools. The proper ventilation and cleansing of schools, rooms and buildings will greatly lessen the danger of the transmission of contagious diseases.

Isolation.—The methods of isolation which are employed in checking the spread of infectious diseases in general can be utilized with much effectiveness in the prevention of scarlet fever. This is true: (1) Because but a very brief period elapses before the appearance of the characteristic eruption, thus making possible an early diagnosis; (2) because the infection is not apt to be transmitted during the first few days of the disease. An opportunity is thus given to separate the patient from other members of the family, who may in this manner be protected. In this respect scarlet fever differs essentially from measles, the contagium of which is given off at a very early date; it is much more difficult to protect persons who have been exposed to a case of measles than those who have been in contact with scarlatina during the early days. The contagious principle of scarlatina is much less diffusible than that of measles. This makes it possible to localize the infection more readily in a portion of a house or a hospital.

In households in which an effective isolation can be carried out, the protection of other members of the family can be accomplished with reasonable assurance. It must be recognized, however, under these circumstances that eternal vigilance is the price of safety. It is a safer plan to remove the well children to another place. The liability of their contracting the disease from an early and brief exposure and then carrying the infection with them is not very great. If there is fear that this will take place they can be detained at home, carefully separated from the patient for a week, which period will fully cover the stage of incubation.

Where effective isolation cannot be carried out at home, and this

is the case in a large majority of households in a community, the patient should be sent to a *hospital*, the whole or part of which is set apart for the treatment of this disease. There can be no doubt that the treatment of scarlet fever in special hospitals is one of the most important means of preventing the spread of the disease. It is possible, with hospital-treated patients, to continue the isolation until every vestige of desquamation has disappeared and until discharges from the nose and ears have ceased. This may in some cases require detention in the hospital for a period of twelve weeks or longer. In patients treated at home, especially among the poor, who are not so apt to recognize the responsibility of their actions, isolation for this period of time can seldom be enforced.

A very large number of cases of scarlet fever are doubtless contracted from patients who are prematurely permitted to associate with others. This naturally brings up the important question: *How long are scarlatina patients to be isolated and quarantined?*

This query is by no means easy of solution. Indeed, in no disease is it so difficult to affirm that the danger of infection has passed. The rule which is commonly followed is to continue the isolation until desquamation has completely ceased and the patient is free from nasal and aural discharges. In the average case this will cover a period of five to seven weeks. In some cases it will be necessary to extend the isolation beyond this period to eight, ten, twelve or even fourteen weeks. Despite the utmost precaution in this respect second cases will at times be infected at a late date.

At present negative cultures of the nose, throat and ears (if discharging) for Streptococcus scarlatinæ are not required by Boards of Health before quarantine is terminated, but this would appear to be a good practice since the examinations are readily made in well-equipped laboratories.

All large scarlet-fever hospitals receive what are known as *return* cases. A certain small proportion, about 2 per cent of the discharged patients, will give rise to cases of scarlet fever in the same household. The early administration of antiscarlet-fever serum, however, is reducing the incidence of return cases because of a more rapid and complete eradication of the infection. The infection may be conveyed by patients who have been in the hospital nine, ten, eleven weeks or longer; this occurs even though desquamation is complete, and the patient antiseptically bathed and clad in perfectly clean garments. The infection in these late cases is probably derived from the secretions of the nose, throat or ears. We have observed on a number of occasions that children who are exposed to the infection at an early period of the disease may escape only to contract the disease from a patient who is supposed to be free of contagion.

Control of Epidemics.—The Dicks[1] have recently stated "that the skin test for susceptibility to scarlet fever used in connection with

[1] Northwest Med., 1926, **25**, 200.

preventive immunization with the toxin and the prophylactic administration of antitoxin, makes possible the control of scarlet-fever epidemics. In an institution where adequate facilities for throat and nose cultures are available it is possible to get the epidemic under control within forty-eight hours.

"The method of procedure in epidemics consists of making skin tests and throat cultures as soon as possible. The throat and nose cultures are made on blood-agar plates which are incubated over night. The next day the skin tests are observed and the persons tested are divided into two groups according to the results of the skin tests. The susceptible persons are separated from the immune.

"Each group is then divided according to the results of the throat and nose cultures. The immune persons who show no hemolytic streptococci in their cultures receive no further treatment. The immune persons, who have hemolytic streptococci in their cultures, are isolated from all susceptible persons on the supposition that they may be immune carriers of scarlet-fever streptococci.

"The susceptible persons are divided into two groups, according to whether or not they have hemolytic streptococci in the throat and nose. Those who show these organisms are regarded as infected, isolated from the susceptible persons who are not infected and given a prophylactic dose of scarlet-fever antitoxin.

"In the susceptible persons who have no hemolytic streptococci in the nose or throat, preventive immunization with the toxin is started. During the course of this immunization they are not allowed to associate with the immune carriers or the infected susceptibles who have been protected by antitoxin nor are they permitted to come in contact with scarlet-fever patients recently discharged from quarantine.

"Since the passive immunity conferred by the antitoxin cannot be depended on to last more than three weeks, active immunization with the toxin may be started two or three weeks after the antitoxin has been given, provided the nose and throat cultures have meanwhile become negative for hemolytic streptococci. It may be that some persons are classed as carriers or as infected who have hemolytic streptococci in their throats that are not capable of producing scarlet fever, but the short incubation period of scarlet fever does not allow sufficient time to test these organisms for specific toxin production.

"In circumstances which do not permit throat and nose cultures it is best to make skin tests and watch the susceptible persons closely for early symptoms of scarlet fever, such as fever and sore throat, and administer the prophylactic dose of antitoxin only if necessary. Administration of prophylactic doses of antitoxin to all the other members of a family when one is attacked by scarlet fever is scarcely justified by the results of skin tests, combined with throat and nose cultures which show that under such circumstances the other members of the family may be immune or not infected."

They have had an opportunity to employ this method of controlling

scarlet fever in 218 families in which scarlet fever had occurred and in epidemics in 4 different institutions. No more work is required than in making Schick tests and cultures on Loeffler's medium for the control of diphtheria, the chief difference being that in the case of scarlet fever blood-agar plates are used instead of the tubes of Loeffler's medium. No microscopic examination of the scarlet-fever cultures is necessary. No new cases of scarlet fever developed in these families or institutions later than forty-eight hours after the control of the epidemic was undertaken, except in instances where for some reason it was not possible to follow the prophylactic administration of antitoxin by active immunization with the toxin before another exposure to immune carriers or the return of the convalescent scarlet-fever patient to the home.

Hygiene of the Sick-apartments.—When a child is stricken with scarlet fever it should be immediately isolated. If it is to be retained at home a room or suite of rooms in the uppermost portion of the house is to be selected as the sick-apartments. Facilities for ventilation should be considered whenever a choice is possible. A room with an open fireplace is to be preferred, although such a convenience is seldom available. An excellent plan is to secure the ingress of fresh air through an adjoining room, the windows of which may be kept open for varying periods according to the season. This room should constitute the avenue of communication with other portions of the house.

Carpets, draperies, ornaments and all dispensable articles of furniture should be removed from the room before occupancy by the patient. The spaces about doors communicating with other portions of the house should be sealed by pasting over them long strips of wrapping paper. Over the door communicating with the corridor should be suspended a sheet which is kept moistened with Labarraque's fluid, a 5 per cent carbolic acid solution or 1 to 1000 solution of bichloride of mercury. Infectious particles floating in the atmosphere will adhere to the moistened sheet.

Great care should be exercised to keep the woodwork, furniture and floors scrupulously clean; this is best accomplished by mopping with cloths saturated with one of the above-mentioned antiseptic solutions.

No one save the person selected to look after the patient should be permitted in the sick room. If the mother acts as nurse she should devote her time exclusively to the patient and should not come in contact with any other members of the family. The nurse should not leave the sick-apartments except after complete change of clothing, bath and shampooing of the hair with an antiseptic solution. Such garments should be worn by the nurse or mother as can be readily boiled or otherwise disinfected. The hair should be protected by a cap in order that it harbor as little infection as possible.

Recognizing that the scarlet-fever contagium is readily carried in clothing and upon various articles, it becomes the duty of the physician to take such precautions as to reduce the liability of transmitting the

disease to a minimum. He should, before entering the sick-room, don a gown which extends from the neck to the feet. A cap should be worn to cover the hair, and it is a good plan, during the desquamative stage to protect the shoes with rubbers. Upon leaving the patients the physician should wash the hands, face, beard and exposed portions of the hair with an antiseptic soap.

Before visiting other children he should endeavor to get a thorough airing out-doors. It is best for physicians who happen to have obstetrical and scarlet-fever patients at the same time to relinquish the care of the one or the other.

That the above precautions are not superfluous is evidenced by the not infrequent carrying of scarlatina by physicians. Murchison investigated this subject and was informed by many physicians that they had conveyed the disease through their infected clothing or upper respiratory tract.

Adult members of a household in which scarlet fever exists should safeguard the interests of others by avoiding contact with the world. The best guide under these conditions is the golden rule.

All articles coming in contact with the patient should be subjected to disinfection. In the room adjoining the sick-aparment should be kept a 5 per cent solution of carbolic acid or lysol which should be used to cleanse utensils, body and bed linen, etc. The linen should be steeped in the antiseptic solution for an hour or two, then wrung out, placed in a receptacle outside the room and finally cleansed with scalding water and laundered.

It is preferable when possible to retain the dishes and eating utensils within the sick-apartments. When they must be sent to other parts of the house to be cleansed they should first be immersed for one-half hour in boiling water.

Discharges from the ears, nose and throat should be received upon pieces of muslin or cheese-cloth, which should be burned or disinfected. Where the sputum cup is used it should contain a solution of carbolic acid or chloride of lime; the same is true of urinals and bed-pans.

Disinfection.—After the termination of the illness the patient should be given an antiseptic bath of 1 to 10,000 bichloride of mercury. The head should be thoroughly washed with antiseptic soap and clean or new clothing put on. It is a wise precaution to prevent association of the patient with other children for several weeks after the quarantine has been raised. The disinfection of the sick-apartments should be carried out with thoroughness. If perfunctory fumigation is relied upon to destroy all infection, unfortunate consequences may follow. The infection of scarlet fever has a remarkable tenacity and may remain resident in articles for months or years. Numerous instances of this are referred to in the section on Etiology.

All articles of little or no value in the sick-room should be burned. This is particularly true of those things with which the patient has been in contact, such as body linen, books and toys.

The apartments should be thoroughly fumigated or sprayed, preferably with formaldehyde solution; as a matter of extra precautions this should be used in greater amounts than that ordinarily prescribed for the given air space.

The floors, woodwork and furniture should be vigorously scrubbed with a carbolic acid solution of about 1 part to 40. The walls, if painted, should be washed with the same solution. If the walls are covered with paper it is wisest to have them scraped and repapered.

Blankets, mattresses, upholstered furniture, clothing, etc., should be disinfected by superheated steam under pressure. Many large cities are now equipped with disinfecting plants to which all such articles may be sent. Where such is not the case the blankets and bed linen after being fumigated had better be boiled and the mattress destroyed by burning.

It is a wise plan, whenever possible, to allow the sick-apartments to remain unoccupied and exposed for some days or weeks to the purifying influence of sunlight and fresh air.

The above precautions may be troublesome and expensive, but it is by careful attention to these matters that attacks of scarlet fever are often prevented and human life and faculties thus preserved.

In the event of death from scarlet fever the body should be enveloped in a sheet wet with a 1 to 1000 solution of bichloride of mercury. It should be placed in a hermetically sealed casket and buried at as early a date as possible. The interment should, of course, be private.

Care of Patient.—Diet.—During the early days of scarlatina, when the fever is high, milk constitutes the best and usually the most acceptable diet. Cool milk is soothing to the throat and assuages the intense thirst which is present in severe cases. Most writers insist upon an exclusive milk diet throughout the entire febrile period, and many counsel its continuance during the early convalescent stage. When the patient is willing to take a sufficient quantity of milk to maintain his body weight there can be no objection to an exclusive milk diet; but some children and many youths and adults object to the monotony of an exclusive milk diet. We have had an excellent opportunity of judging of the effect of diet in scarlet fever. For many years the scarlatina patients in the Philadelphia Hospital for Contagious Diseases received an exclusive milk diet during the febrile period. For a period of eight months, during which time over 500 patients were treated, the patients had a more liberal dietary. They were encouraged to drink plenty of milk, but were permitted as soon as they cared to, to have bread and butter with their meals and a simple pudding and stewed fruit once a day. We found that patients desired nothing but the milk while the temperature was high, but that when it became lower they were eager to obtain bread and butter in addition. Our patients appeared to progress just as well under the enlarged dietary. Urinary examinations were made every other day and the results compared with those under the exclusive milk diet.

Albuminuria was not more frequent in the former than in the latter and the renal complications altogether were of a mild character. We present these facts for what they are worth. It is a hardship for some patients to be denied solid food for weeks, and they may as a result receive an insufficient amount of nourishment. We have never seen the above diet do any harm.

Caiger[1] allows patients, during the febrile stage, milk with eggs beaten up, broths and calves-foot jelly. When the temperature falls he permits eggs, custard, light puddings and bread and butter. Ripe and succulent fruit is given at any time throughout the illness. Caiger states that there is no risk, as has been alleged, of inducing a nephritis by permitting these articles of food to be taken.

Our present practice is to use an exclusive milk diet in infants and very young children and in cases of nephritis, but to allow older children and adults a little more latitude. The latter frequently request light solid foods, and we believe that when there is an appetite for such articles they do no harm.

Confinement to bed should be enforced during the febrile period and during cold and inclement weather, in severe cases for a week or more after the subsidence of the fever. Young and restless children whose actions cannot be well controlled had better be kept in bed from three or four weeks, or until the liability of nephritis has passed.

While it is generally believed that "catching cold" has been greatly exaggerated as a factor in nephritis, Griffith states that chilling of the surface certainly acts as a powerful accessory cause in the production of complications.

The detention of the patient in his bed or room will be influenced by the age of the individual, the season and other factors which the discretion of the physician must solve.

In view of the liability to kidney complications, it is necessary to keep the skin, which is an important eliminatory organ, in a functionally active state. All clinicians are agreed as to the advisability of employing sponge baths; tepid water is preferably used and should be applied twice daily. In addition to promoting gentle diaphoresis these baths subserve the ends of comfort and cleanliness.

To lessen the tension of the skin and allay itching the inunction of some unguentous substance is desirable. We have for years employed cacao butter for this purpose and have found it cleanly and agreeable alike to nurses and patients. When much itching is present a 1 per cent menthol or 2 per cent carbolic ointment may be used.

Inunctions of salves containing oil of eucalyptus, ichthyol, certain silver salts and many other substances have from time to time been lauded as possessing special therapeutic virtues.

Medical Treatment.—It must be frankly admitted that we possess no medicament capable of directly influencing or abridging the course of scarlet fever. Our therapeutic efforts must be directed toward

[1] Loc. cit., p. 170.

combating excessive development of the symptoms and toward preventing and modifying complications. The drug treatment is, therefore, purely symptomatic in character.

In *mild* cases of scarlet fever special medication is often unnecessary, the disease progressing to a favorable termination under the influence of proper hygienic care and nursing.

During the febrile stage it is customary to administer a febrifuge mixture. We have been in the habit of using a combination of the liquor ammoniæ acetatis and sweet spirit of nitre, sweetened with a little syrup.

Vomiting, when present, may be controlled by abstinence from food and the administration of fractional doses of calomel. Constipation may be corrected by the latter drug or one of the mild vegetable laxatives.

It is advisable to use some mild antiseptic in the throat, not only to relieve the congestion and soreness, but to lessen secondary infection and the liability of extension of inflammation to the middle ear.

Fever.—There are many cases in which attention must be directed to the control of high temperature and the accompanying nervous phenomena. Scarlet fever is frequently characterized by a very high initial pyrexia, which tends in a few days to defervesce. When the fever is above 103° F., and particularly when there are severe nervous symptoms, such as headache, delirium, stupor or convulsions, antipyretic measures should be employed. In the reduction of temperature preponderant reliance is now placed upon *hydrotherapy*, although the prompt administration of an adequate dose of antiscarlet-fever serum is usually sufficient. Different clinicians have individual preferences as to the mode of applying water; the methods in vogue are tepid sponge baths, cold sponge baths, wet or cold packs, and warm, graduated, or cold tub baths. Ice-bags and Leiter's coils are also employed.

The routine treatment of scarlet fever with cold tub baths, as in the case of typhoid fever, has not met with general favor. They may be employed in cases accompanied by great hyperpyrexia, provided there is no pronounced cardiac depression. Cold baths are not borne well by infants or very young children, and should not be used in such cases.

In cases of average severity with high fever, sponging with cold water, with or without alcohol, will usually suffice to keep the temperature within proper bounds. If this does not control the fever and nervous symptoms resort may be had to the cold pack, which has a more pronounced antipyretic influence. In milder cases it may be all sufficient to keep an ice-bag or cold coils applied to the head.

Warm tub baths of about the temperature of 95° F. are recommended by many physicians. These will frequently reduce a high temperature, and are more acceptable to the patient and the members of his family than cold baths; or the graduated bath may be used, the temperature gradually being lowered until the desired reduction in the fever is accomplished.

The old superstition about baths being dangerous and causing patients to "catch cold" has been dissipated, and a complete unanimity of sentiment now exists among physicians as to the desirability of using baths of one kind or another in scarlet fever.

Medicinal antipyretics are used to a very limited extent nowadays. The general feeling is that they are dangerous in large doses and ineffective in small amounts. Phenacetin in small doses (2 or 3 gr.) may be given as an adjunct to hydrotherapy in bad cases, or to relieve headache and nervous symptoms in milder cases.

Throat.—Where the throat shows but slight involvement mild antiseptic fluids may be employed, either in the form of a spray or a gargle. For this purpose a weak Dobell solution or a solution of boric acid or chlorate of potash may be employed. Very young children cannot use a gargle, and often vigorously object to efforts at swabbing or spraying the throat. Where the physical resistance is so pronounced as to exhaust the child the procedure is of doubtful advantage and had better be discontinued. In the anginose variety of the disease it is equally important to cleanse the nares and throat and to avoid an exhausting resistance. A firm and skilful nurse is of great assistance under such circumstances.

When the throat is severely involved and a streptococcus pseudomembrane is present, systematic and vigorous treatment is indicated. Not only does the pharyngeal inflammation tend to spread to the nares and middle ear, but a general infection is apt to result from streptococcic absorption.

In these cases the throat should be frequently sprayed with peroxide of hydrogen, plain or diluted, according to the age of the patient and the degree of inflammation present in the fauces.

In septic cases with ulceration of some of the soft tissues, Caiger[1] speaks in terms of high praise of a strongly acid solution of chlorate of potash containing a large amount of free chlorine.[2] The throat and nose are irrigated with this fluid by means of a soft-rubber syringe with a vulcanite nozzle, the head being held over a basin with the mouth kept open.

Caiger says: "No amount of gargling, spraying or swabbing can compare with it (this method) in point of efficacy."

Forchheimer speaks highly of direct application to the throat by means of a swab saturated with Loeffler's iron-toluol solution. This should be applied once or twice a day and held in contact with the diseased parts for a little while to secure the best results. In cases of extensive streptococcic exudate in the throat this writer counsels the use of antistreptococcus serum, which, he believes, will occasionally improve the local symptoms in a remarkable manner.

[1] Loc. cit., p. 171.

[2] According to Caiger the solution is prepared by pouring strong hydrochloric acid upon powdered chlorate of potash in a large, stoppered bottle. The proportions advised are 5 minims of strong acid to 9 gr. of the salt, with sufficient water to make an ounce. The solution is of a greenish color and has a strong chlorine odor.

Purulent Rhinitis.—Purulent rhinitis in scarlet fever is apt to accompany severe throat involvement. The extension of the suppurative inflammation to the nasal mucous membrane increases the liability to general sepsis and augments the gravity of the disease. A sanious, seropurulent discharge issues from the nostrils in great quantities. The efforts of the nurse must be directed toward systematic and frequent cleansing of the nasal cavities. But this must be done with great care and gentleness. The forcible projection of liquids into the nose will do harm, as will, likewise, the use of strong and irritating antiseptics. It has been our custom to have the nose gently irrigated with a warm saline solution; this is done with a small glass piston syringe with a blunt end. In obstinate cases we have employed a 10 per cent solution of argyrol or one of the newer silver compounds. This remedy has lessened the profuse discharge and has led to a healthier condition of the parts.

Patients with gangrenous destruction of the soft palate or tonsils do not, as a rule, recover. Apart from the stronger remedies referred to in the treatment of membranous angina, one may, in this condition, employ a warm solution of permanganate of potash, 1 to 2000. In circumscribed gangrenous patches we have frequently applied the tincture of iodine with good results.

Noma.—Noma is fortunately an uncommon complication of scarlet fever. When the condition is still in its incipiency the pultaceous deposit upon the mucous surface should be scraped away with a curette and the base thoroughly cauterized with fuming nitric acid. This had better be done under the use of ether, which can be given in just sufficient quantity to benumb the patient's sensibilities. If the cutaneous surface becomes attacked free excision will be found to be a not too radical procedure.

Glands.—The glands at the angle of the jaw commonly attain the greatest size and are the most frequent to undergo suppuration. Glandular abscess may be expected in nearly all cases of anginose scarlatina. In the beginning an ice-bag should be applied about the neck. A special bag manufactured for this purpose buttons around the neck and keeps the ice in close apposition with the affected glands. A piece of flannel should be interposed between the bag and the skin.

If, despite the application of cold, the gland increases in size and suppuration becomes inevitable, heat should be substituted. Flaxseed poultices, rendered antiseptic by having incorporated in them a 1 to 4000 solution of corrosive sublimate, hasten the suppurative process. Upon the first suspicion of pus formation an incision into the gland should be made and free drainage established. It is better to lance prematurely than to delay too long, for inflammation may spread to the periglandular tissues. When cellular infiltration takes place free incisions should be made, even though no pus focus can be demonstrated, for by this means the deep-burrowing pus which forms later

may be anticipated and the most fatal of complications—Ludwig's angina—may be prevented.

The Ears.—Inasmuch as otitis media is an extremely common complication of scarlet fever, it should be guarded against as much as possible and the condition promptly met when it develops. The prophylactic treatment relates to those measures which are designed to keep the naso-pharynx clean and free of infective secretions. While this object is a laudable one, no treatment will, in bad cases, prevent the development of otitis media. Indeed, it may be stated that the liability to ear complications is directly proportionate to the severity of involvement of the throat and nose.

Pain in the ear is best relieved by the application of heat; this may be accomplished by syringing gently with water as hot as can be borne, or, better still, by the use of external dry heat. The hot-water bag or hot-salt or bran bag may be placed against the ear. Dench suggests heating a little salt in the tip of a kid-glove finger and thrusting the same into the ear. The instillation of a few drops of a warm 4 per cent solution of cocaine is advised by some writers.

When the pain continues despite these measures suppuration is probable. If upon inspection of the tympanic membrane bulging is seen, an incision should be made to evacuate the pus. It should be remembered, however, that in very young children, in whom otitis is commonest, the small size of the canal and the restlessness of the patient make aural inspection and paracentesis extremely difficult and unsatisfactory. Furthermore, spontaneous rupture is the rule in these cases, and may be the first evidence of involvement of the ears.

After drainage is established it is necessary to keep the external auditory meatus clean and free of pus. Various liquids are advised, such as 1 to 5000 solution of bichloride of mercury, 1 in 4 solution of peroxide of hydrogen, saturated solution of boric acid, etc. We have found boiled water containing a little carbolic soapsuds very useful. All solutions should be used warm and injected gently with a soft-rubber bulb ear syringe. The meatus should not be plugged with cotton. Sudden rise of temperature indicates a stoppage of drainage or extension of inflammation to adjacent structures. Any swelling in the mastoid region should be promptly and freely incised and proper drainage maintained. There should be no hesitancy about entering the mastoid antrum if the bone exhibits evidence of disease. In all such cases the services of an aural surgeon should be called into requisition.

Vaccine Treatment of Otitis and Rhinitis.—As shown by Weston and Kolmer,[1] the treatment of otitis media with carefully prepared autogenous vaccines materially shortens the average course of the disease and lessens the incidence of mastoid infections and "return cases." We believe that it is a good routine practice to culture a discharging ear early and to prepare and keep in readiness an autogenous vaccine for administration if there is a tendency to prolonged suppuration.

[1] Jour. Am. Med. Assn., 1911, **56**, 1088.

Kolmer and Weston[1] have also found that autogenous vaccines are of aid in the treatment of septic rhinitis of scarlet fever, since they materially shorten the time for recovery and aid in decreasing the number of "return cases."

Joints.—Scarlatinal synovitis or arthritis (scarlatinal rheumatism) calls for both local and constitutional treatment. Physicians are not all in accord as to the value of the salicylates in inflamed joints in this disease, although many testify to their efficiency. Where the joint involvement is pronounced they should be given a trial; if no improvement is noted, or if the stomach is deranged or the heart depressed, their administration had better be interrupted. The inflamed joints should be painted with tincture of iodine, surrounded by cotton-wool and bandaged with a flannel bandage. Increase of fever, chills and sweats, with aggravation of the local symptoms, indicate the presence of pus in the joints. The joints should be incised, through-and-through drainage established and the cavity washed out with antiseptic solutions. When there is doubt as to the presence of pus the aspirating needle may be used and a small quantity of fluid drawn out. When streptococci are present in the synovial fluid the intramuscular injection of antiscarlet-fever serum is advised. During convalescence from articular complications care should be taken to preserve the mobility of the joint by gentle massage and passive movements. In all cases of joint involvement the heart should be carefully watched, for cardiac complications are much more common under these circumstances.

Kidneys.—Nephritis is one of the most common and most serious complications of scarlet fever. It not infrequently occurs in mild cases, at a time when the patient is considered almost well. It is a good plan to keep patients in bed for at least three weeks, as it is during the third week of the disease that nephritis is most frequently discovered. The urine should be examined each day for both albumin and tube casts. Ordinarily the chemical and microscopic examinations of the urine will enable one to determine the onset of a nephritis. In rare cases sudden and alarming symptoms may develop without the previous occurrence of albuminuria. It is of importance, where nephritis is suspected, to have the quantity of urine excreted in each twenty-four hours carefully measured. Pallor, puffing of the face and elevation of temperature are among the early clinical evidences of oncoming nephritis. Baker[2] has found that the wheal following the *intracutaneous injection* of 0.2 cc. of 0.8 per cent solution of sodium chloride, as described by McClure and Aldrich,[3] disappeared in from fifty to ninety minutes in normal persons and those convalescent from scarlet fever. But in severe cases of the disease during the first few days the disappearance time was from three to thirty minutes despite the absence of clinical edema; in moderate average cases it was from thirty to fifty

[1] Am. Jour. Med. Sci., September, 1911.
[2] Jour. Am. Med. Assn., 1924, **83**, 1566.
[3] Ibid., 1923, **81**, 293.

minutes during the first week. From a study of 70 cases he concluded that the disappearance time is generally reduced and that the rapidity of reduction parallels the severity of the disease and aids in estimating the condition of the patient.

When albumin is found the patient should be kept in bed and the temperature of the room kept warm and equable. The diet should be restricted to milk, which, with water, the patient should be encouraged to drink in large quantities. The bowels should be kept freely open and the action of the skin encouraged by daily warm baths. Under this simple regimen the vast majority of cases will make a good recovery.

If the urine is reduced in quantity and the symptoms do not improve, a more active treatment should be pursued. We have found the use of a diuretic mixture containing infusion of digitalis and acetate of potash of especial value. Calomel may be given in sufficient dosage—about $\frac{1}{4}$ gr. three times a day—to produce two or three movements a day; this drug has the advantage of increasing renal secretion at the same time. It is an excellent plan to place over the kidneys a warm poultice composed of 1 part of ground mustard to 15 parts of flaxseed meal. This should be renewed every two or three hours.

Vomiting, flushed face, and a high-tension pulse indicate the use of nitroglycerin. This drug may be administered to children in the dosage of $\frac{1}{300}$ to $\frac{1}{200}$ gr. every few hours until the physiological effect is produced.

The development of uremic symptoms, such as twitchings, delirium or stupor necessitates vigorous treatment. Free but not excessive catharsis should be produced by salines. The patient should be given a *hot pack* or a *hot-vapor* or *hot-air bath*. In using the pack the patient is enveloped in a blanket which is wrung out of water of 100° F. temperature; this is surrounded by a dry blanket and this in turn by a rubber mackintosh. After free sweating is induced the blankets can be removed and the patient rubbed dry. The hot pack may be used twice a day.

In the hot-air bath the patient is enveloped in blankets between the folds of which are placed hot bricks or bottles. Where these measures do not suffice pilocarpine may be given hypodermically. The dose varies from $\frac{1}{60}$ to $\frac{1}{12}$ gr. according to age; for a child aged five years $\frac{1}{30}$ gr. may be given. Owing to the frequent depressing effect of this drug in children its administration had better be preceded or accompanied by stimulation. It is advised that pilocarpine be withheld in cases in which there is profuse bronchial secretion, to avoid a possible pulmonary edema.

If convulsions develop the hydrate of chloral should be given either by the mouth or bowel. A hypodermic injection of morphine is often of great value. If the convulsive seizures are persistent they should be controlled by inhalations of chloroform. In desperate cases it is well to perform venesection and follow the abstraction of blood by the intravenous injection of salt solution.

Alarming symptoms may result from edema of the lungs or from effusion of serum into the pleural or pericardial sac. These conditions must be borne in mind and carefully watched for.

A certain degree of anemia is apt to follow severe cases of nephritis. For this condition iron in the form of Basham's mixture will be found to serve a useful purpose.

After a severe nephritis great care should be exercised concerning the patient's diet and hygiene. The urine should be carefully examined at frequent intervals. If albuminuria persists and becomes subacute the child should, if possible, be sent to a warm climate, where he should remain during the winter months. Every precaution should be taken to protect the patient against exposure.

The Heart.—In severe cases of scarlet fever it is frequently necessary to support a flagging heart. When the first sound is weak or the pulse is rapid, small or irregular cardiac stimulation is imperative. The majority of cases of scarlet fever will not require the use of alcohol, but one should not hesitate to use a good brandy or whiskey in full doses when the heart gives evidence of failing power. Digitalis will serve a useful purpose when the stomach is tolerant. When digitalis is not well borne strophanthus may be substituted. Strychnine in $\frac{1}{200}$ to $\frac{1}{100}$ gr. doses will often be found valuable. When the peripheral circulation is feeble resort may be had to hypodermics of nitroglycerin, gr. $\frac{1}{300}$ to $\frac{1}{200}$ every few hours. The subcutaneous injection of camphor dissolved in ether or almond oil may tide over a threatened collapse.

Endocarditis and pericarditis develop most commonly in association with scarlatinal rheumatism. Involvement of the joints should cause one to be vigilant concerning cardiac complications. Upon the first suspicion of valvular trouble an ice-bag should be placed over the heart and the salicylates should be cautiously administered or continued if they were previously being used. The patient should be kept at perfect rest in a horizontal position. We have seen sudden dilatation of the heart result from the patient sitting up. If pericarditis with effusion is present it may become necessary to attempt an evacuation of the pericardial fluid.

Gastro-intestinal Tract.—The early vomiting is seldom persistent; when treatment is necessary abstinence from food, the swallowing of pellets of ice and the administration of fractional doses of calomel will control the emesis. Early diarrhea need not be interfered with if it is mild. If it is severe it may be controlled by the use of bismuth, vegetable astringents and, if necessary, opium. The same treatment should be applied to profuse bowel movements developing late in the disease. If the inflammation is in the large intestines irrigation of the colon with a warm saline solution or mild astringents and antiseptics will be found useful.

Purpura.—Hemorrhages into the skin and from the nose, mouth, kidneys, bowels, etc., may develop during the second or third week of scarlet fever. The patients become extremely anemic and may die

from the loss of blood. In a case under our care of purpura with epistaxis and bleeding from the mouth and kidneys, the patient gradually going from bad to worse, rapid improvement followed the administration of turpentine. Five minims of turpentine were given in an emulsion of acacia and elixir of orange, every two or three hours. The hemorrhage stopped in less than a day and the patient made a good recovery, the previously existing nephritis not being aggravated by the turpentine. This drug is highly recommended in purpura by Crocker, of London. Ferruginous preparations are indicated in the anemia that follows these attacks. In severe cases the *intramuscular* injection of human serum or blood is recommended. For adults the dose may be 20 cc. and repeated if necessary. Blood transfusion is sometimes required. The intramuscular injection of 5 cc. of sterilized milk every three days is also sometimes effective.

Malignant cases of scarlet fever, characterized by a mottled and cyanotic surface, cold extremities, with or without high internal fever (as indicated by the rectal temperature), require vigorous stimulation. A hot mustard bath should be given to increase the peripheral circulation and lessen internal congestion. Trousseau counselled the use of ammonia and musk in this condition. Jacobi advises the use of ammonia, musk and camphor, and considers these drugs superior to alcohol. He also recommends in these cases, when the temperature is low, the use of morphine in doses of $\frac{1}{50}$ to $\frac{1}{20}$ gr., repeated according to effect.

In malignant attacks and also when uremia is threatened it is advisable to employ *subcutaneous* or *intravenous injections* of a *decinormal saline solution* (0.6 per cent solution of sodium chloride in sterilized water); 200 to 500 cc. may be injected in a child. In uremia the injection may be preceded by venesection.

Chemotherapy in Scarlet Fever.—Numerous reports by Lenzmann,[1] Laques,[2] Klemperer and Worta,[3] v. Boltenstern,[4] Lenzman,[5] Glaser[6] and others indicate that intravenous injections of arsphenamine or neoarsphenamine may be distinctly worth while in the treatment of severe cases, as it would appear that the temperature is lowered along with a reduction in the incidence of complications and mortality. Since these arsenicals have been reported upon favorably in the treatment of other streptococcic infections and especially puerperal sepsis, they may be worth while using alone or especially in conjunction with the Dick or Dochez serum in the treatment of unusually severe cases. The dose of either for children may be from 0.1 to 0.3 gm. and for adults 0.5 to 0.6 gm. by intravenous injection; apparently arsphenamine (disodium salt) has given better results than neoarsphenamine.

[1] Med. Klin., 1912, vol. **9**, No. 16.
[2] Therap. d. Gegenw., 1912, **53**, 383.
[3] Ibid., 198.
[4] Ztschr. f. Chemotherap., 1914–1915, vol. **3**.
[5] Therap. d. Gegenw., 1914, **55**, 243.
[6] Deutsch. med. Wchnschr., 1913, **40**, 1755.

Young and Birkhaug[1] have recently reported the successful treatment of an unusually severe case of scarlet fever complicated with erysipelas and septicemia, by intravenous injections of mercurochrome, and this compound may be quite worthy of trial in severe cases of scarlet fever, especially those showing the presence of large numbers of streptococci in the blood. As shown by Hirschfeller,[2] ethyl-hydrocuprein has no effect upon either scarlet fever or measles.

[1] Jour. Am. Med. Assn., 1924, **83**, 492.
[2] Am. Jour. Dis. Child., 1916, **2**, 361.

CHAPTER IX.

MEASLES.

Definition.—Measles is an acute, contagious, febrile disorder, characterized by catarrhal symptoms affecting the upper respiratory tract, and an eruption of dusky-red, slightly elevated macules. The disease commonly occurs in epidemics and attacks for the most part children; one attack confers immunity in the vast majority of cases.

Synonyms and Derivation.—*Rubeola, morbilli;* French, *la rougeole;* German, *masern, flecken;* Italian, *morbilli, rosalia*; *Spanish; serampion.*

The word measles is probably derived from an old English word, *maseles*. Hirsch calls attention to the resemblance to the German *masern* and the Sanskrit *masura*, meaning spots. The term *morbilli* is derived from the Italian *morbillo*, which signifies the *little disease*. This diminutive was doubtless employed to distinguish measles from smallpox, the plague, *il morbo*, probably referring to the latter affection.

History.—It is impossible to state with any degree of positiveness the date of origin of measles. The first clear mention of measles is attributed to that master Arabian physician, Rhazes, who lived about 910 A.D. The term *rubeola* was later brought into use by the Latin translators of the Arabian writings. Morbilli was very loosely applied to many exanthematous conditions.

The Arabian physicians regarded measles as a variety of smallpox.

To Sydenham (1660–1674) belongs the distinction of trenchantly separating smallpox and measles. But scarlatina and measles were still confounded.

As far as any accurate knowledge is concerned, measles is a disease of comparatively modern origin.

THE ETIOLOGY OF MEASLES.

Transmission of Measles.—Measles may be regarded as the most contagious of the various exanthematous affections. When it breaks out in a household or an institution it is almost impossible to prevent its spread, so diffusible is the contagious principle which causes it. This fact and the universal susceptibility to the disease make measles the commonest malady to which human flesh is heir. But few persons go through life without at some time or other passing through an attack of measles. When it is escaped during childhood it is extremely apt to be contracted during adult life; in this respect it differs markedly from scarlatina, against which most adults acquire an immunity.

Whether or not measles can be successfully *inoculated* still remains in doubt, despite the very considerable experimentation and literature on the subject.

In 1758 Francis Home, of Edinburgh, attempted the inoculation of measles at the suggestion of Monro. He saturated bits of muslin with blood obtained by incising through the measle lesions. These were laid open upon the excoriated arms of healthy persons. In this manner he claims to have inoculated 12 children, in most cases with success, although the disease appeared in a mild form. Pieces of muslin moistened with the nasal secretion which were placed in the nostrils of healthy children failed to produce the disease. Theussink,[1] who attended Home's Clinics and saw these experiments, expresses doubt as to Home's interpretation of the results. At Theussink's suggestion, his friend Themmen later repeated these inoculations in 1816 with negative results.

In 1822 Speranza successfully inoculated measles, and claims to have had the disease himself in this manner. In 1854 an Italian physician, Bufalini, reported successful results both of his own and his countrymen, Locatelli, Rossi and Figueri; Horst and Percival are likewise credited with positive inoculations.

In 1842 Katona[2] performed 1122 inoculations in 26 townships of the Borsoder Comitates; 93 per cent of these were successful, the attacks being of a mild character. An admixture of blood and the contents of miliary vesicles taken at the height of the rash was rubbed into excoriations made after the manner of vaccination. At the end of seven days fever and the usual prodromal symptoms developed; the eruption appeared two or three days later, about the ninth or tenth day after the inoculation.

Mayr successfully inoculated measles in 1848 and in 1852. He placed freshly secreted nasal mucus from a case of measles in the nostrils of two children living at a distance from one another. At the end of eight and nine days, respectively, catarrhal symptoms developed, followed in a few days by fever and the eruption. In an article on measles[3] published in 1866, Mayr remarks: "Inoculations with blood made by myself in 1848 and 1852 afforded negative results." The use of desquamating skin also failed to transmit the disease, as had previously occurred in the experiments of Alexander Monro. The negative results in the transmission of measles by the inoculation of blood, in the hands of Themmen, Albers, Mayr and Thomson, should cause us to accept the alleged successful results with some reservation.

But that the virus does occur in the blood of measles patients is indicated by the results of its experimental transmission to two human

[1] Abhandlung über die Masern, translated from the Dutch by Dr. Doden, of Göttingen.

[2] Nachricht von einer im Grossen erfolgreich vorgenommenen Impfung der Masern während einer epidemischen Verbreitung derselben, Osterreich. med. Wchnschr., 1842, No. 29, p. 697.

[3] Mayr: Measles in Hebra's Disease of the Skin, 1866.

volunteers by Hektoen[1] in 1905 and to monkeys and rabbits as reviewed later. Also by the accidental transmission of the disease in emergency *blood transfusions.* This seems to have been the case at the Minneapolis General Hospital, where for purposes of life-saving transfusion, in two instances, the blood from a mother subsequently discovered to have measles was injected into the circulation of her child and produced characteristic measles as reported by Bauguess.[2] Contact infection was excluded. The virus was found to be present in the blood at least two days before the appearance of the rash. Owing to the definiteness of the time of inoculation, the incubation period could be accurately established at thirteen and fourteen days. Since measles may be transmitted through transfusion of blood, Dr. Bauguess regards it as advisable to take a careful history of those who are to be blood donors for young patients, and to look for Koplik spots. Harrell[3] also records a case of accidental transmission of the disease by blood transfusion.

The usual mode of contagion in measles is by *direct exposure* to a person suffering from the disease. The contagium of measles differs from that of scarlet fever in two respects—it is *more diffusible* and it is *less tenacious;* the infection does not tend to any marked degree to cling to objects or apartments, and transmission of the disease by fomites is, therefore, distinctly unusual.

Richard[4] claims that the contagium of measles cannot be carried by fomites nor by a protected person. Bard[5] states that the contagium of measles does not remain viable in a locality from which patients have removed. Comby[6] says that the germ of measles has but little vitality outside of the body, and that every germ that emanates from a measles patient is dead at the end of a few hours.

While we are not prepared to dogmatically state that measles cannot be carried by infected objects or third persons, our experience is in accord with that of most writers that such occurrences must be very rare. Von Kerchensteiner calls attention to the observation that physicians' children do not as a class contract measles earlier in life than other children. Considering the frequent neglect of precautionary measures, this would not be the case if the disease were readily transmissible through infected garments.

Official reports of the extensive epidemic of measles in the Faroe Islands in 1846 (at which time over 6000 persons were attacked) gave no instances of transmission of the disease by infected articles or by third persons, and this point was carefully investigated by the physicians who studied this epidemic.

Theussink states that he knew of a case where the infection was

[1] Jour. Infect. Dis., 1905, **2**, 238; Jour. Am. Med. Assn., 1919, **72**, 177.
[2] Am. Jour. Dis. Child., 1924, **27**, 356.
[3] Jour. Am. Med. Assn., 1924, **82**, 1812.
[4] Therap. Gaz., July 16, 1888.
[5] Revue d'hygiéne et de Pólice Sanitaire, May 20, 1891.
[6] Traité des mal. de l'enfance.

conveyed by a letter sent through the post, and also an instance where it was attributed to an engraving sent by mail. The negative evidence of intermediate infection is so abundant that such cases must be substantiated beyond the peradventure of a doubt before they can be unreservedly accepted.

When measles breaks out in a family circle it attacks all of the susceptible members thereof. Kindergartens and schools offer fertile opportunity for the dissemination of diseases. Consequently measles, as well as the other contagious diseases of children, is much more common during the periods of the year that these institutions are in session.

Transmission of Measles to the Lower Animals.—The view is held by some veterinarians that measles may attack certain of the lower animals. Behla,[1] of Luckau, Germany, claims to have produced in a young pig a disease closely resembling measles by inoculating the nose, mouth and throat with mucus from the nose and mouth of a child suffering from measles. Four days later the pig developed a discharging nose and congested and watery eyes. On the fifth day the animal was sick, had a temperature of 103° F., shivered and refused food. On the eighth day the non-hairy portions of the face showed red spots, which spread in another day over the body, being followed by a mild desquamation. Two pigs that had been exposed to the first one developed similar symptoms in the course of two weeks. The attendant regarded the disease as swine fever, but examination of the blood and mucus failed to show the presence of the bacillus found in this disease.

Josias[2] failed to confirm the results obtained by Behla, but succeeded in communicating the disease to monkeys. Chavigny[3] also observed measles in a monkey.

Anderson and Goldberger[4] and Blake and Trask[5] likewise successfully infected monkeys experimentally and Degkwitz[6] states that they are susceptible to filtrates of naso-pharyngeal secretions of measles patients.

Furthermore it would appear that guinea-pigs may be susceptible, since Duval and D'aunoy[7] found that after a definite incubation period following intracardiac injections of blood from cases of measles, that a reaction of leukopenia fever and nephritis followed. But rabbits appear to be more susceptible, since Nevin and Bittman,[8] Hardie,[9] Duval and D'aunoy,[10] Tunnicliff and Moody[11] and Scott and Simon[12] claim to have successfully infected them with material from human

[1] Centralbl. f. Bakteriol. u. Parasitol., **20**, 16, 17. Quoted by Williams: Twentieth Century Practice of Medicine, p. 123.
[2] La méd. mod., 1898, No. 29.
[3] Bull. méd., 1898, **12**, 334.
[4] Pub. Health Repts., 1911, No. 26.
[5] Jour. Exper. Med., 1921, **33**, 385.
[6] München. med. Wchnschr., 1926, **73**, 281.
[7] Jour. Exp. Med., 1922, **35**, 257.
[8] Jour. Infect. Dis., 1921, **29**, 429.
[9] Compt. rend. Soc. de biol., 1921, **74**, 968.
[10] Jour. Exper. Med., 1922, **36**, 231, 239.
[11] Jour. Infect. Dis., 1922, **31**, 382.
[12] Am. Jour. Hyg., 1924, **4**, 559, 725; 1925, **5**, 109.

cases of measles, although Purdy[1] states that he failed to infect these animals but was successful with monkeys. Apparently a sustained pyrexia occurring at a certain time, coupled with an amphophilic leukopenia, constitute the most constant symptoms in rabbits. With these criteria Scott and Simon claim to have demonstrated the virus in the blood of measles patients up to the nineteenth day of the disease and on the mucous membranes up to the seventh day.

Bacteriology of Measles.—Various cocci, bacilli and protozoa have been claimed from time to time to be the specific cause of measles. That an infectious agent is present cannot be denied, but neither can it be said that the germ has been positively isolated and identified.

Tunnicliff[2] regards a filter-passing, Gram-positive green-producing diplococcus isolated from the blood in special mediums as the specific agent; Perry and Fisher[3] also found a similar toxin producing organism in the blood designated as Streptococcus morbilli, but differing from that of Tunnicliff in being aërobic; Long and Cornwell[4] failed to secure these organisms in blood cultures of 26 cases. Both Tunnicliff and Ferry have reported positive skin reactions in susceptible individuals following the intracutaneous injection of the soluble toxins of the organisms. Negative reactions were reported as occurring in the majority of persons who have had the disease and both have claimed that the toxins were neutralized in the test-tube by the addition of measles convalescent serum.

Caronia,[5] on the other hand, claims that the Gram-negative filter-passing diplococcus which he has isolated from the blood, naso-pharynx and tissues of cases of measles and experimentally infected rabbits is the cause of the disease, and his work has been apparently substantiated by Arloing and Dufourt,[6] Ritossa,[7] Auricchio,[8] Sindoni,[9] Saliroli[10] and other Italian investigators, although Takaki,[11] Szirmai and Jacoborics,[12] Meyer,[13] McCartney[14] and others have been unable to confirm it.

Degkwitz[15] states that a filter-passing virus is the cause which he has been able to cultivate artificially but without being able to see the organism. His investigations successfully repeated Hektoen's human inoculation experiment, and he then attempted to discover whether the virus could be cultivated. Virus was obtained by bleeding a child on the first day of the eruption in a typical case of measles, and diluted with a special salt solution containing the same number of anions and

[1] Brit. Jour. Exper. Path., 1925, **6**, 210.
[2] Jour. Am. Med. Assn., 1917, **68**, 1028; 1918, **71**, 104. Jour. Infect. Dis., 1918, **22**, 402; 1919, **24**, 76, 181; 1925, **37**, 193.
[3] Jour. Am. Med. Assn., 1926, **86**, 932.
[4] Jour. Infect. Dis., 1927, **40**, 408.
[5] Pediatria, 1923, **31**, 801.
[6] Compt. rend. Soc. de biol., 1924, **90**, 763.
[7] Pediatria, 1924, **32**, 346.
[8] Rev. d. clin. pediat., 1924, **22**, 755.
[9] Pediatria, 1924, **32**, 888.
[10] Ibid., 1925, **33**, 737.
[11] Wien. klin. Wchnschr., 1926, **39**, 325.
[12] Jahrb. f. Kinderh., 1926, **111**, 331.
[13] Monatschr. f. Kinderh., 1926, **31**, 270.
[14] Lancet, 1927, i, 93.
[15] Deutsch. med. Wchnschr., 1924, **50**, 374; München. med. Wchnschr., 1926, **73**, 181; Jour. Infect. Dis., 1927, **41**, 304.

cations as the blood, and of the same pH. One cubic centimeter of a 1 to 5000 dilution failed to produce measles in a child known to have never had measles. From this dilution subcultures were made over a period of seventy-eight days, during which time the subcultures had gone through fifteen generations and a dilution of 1 in 3 trillions of the original virus had been reached. The cultures were made in symbiosis with green cocci, sometimes the Tunnicliff organism and sometimes pneumococci. One cubic centimeter amounts of the final subculture, after filtration through a Berkefeld W filter, were injected into various persons, and produced reactions consisting of a rise in temperature, conjunctivitis, bronchitis and rhinitis from ten to fourteen days after inoculation. Sometimes bluish-red macules appeared on the skin, but never a typical measles eruption. Control injections of the symbiotic organisms carried through in the same way alone did not produce any recognized reaction. Two months later inoculation of both groups with infectious measles blood was followed by the appearance of typical measles in those persons who had previously received only the filtrate of the symbiotic organisms. Those previously inoculated with subcultures of the virus did not contract the disease.

In his experiments on monkeys Degkwitz was not able to produce a rash which he regarded as typical of measles, but he showed that the serum of those monkeys developing a rise in temperature after receiving doses of virus had definite value in protecting persons against doses of virus of proved infectivity. Degkwitz has advocated the use of a protective measles antiserum, made presumably by inoculating animals with repeated doses of his virus. Reports of its use have not been uniformly favorable.

If the human inoculation experiments of Degkwitz are repeated and confirmed, one new fact, the ability of measles virus to grow outside the body, will have been added to the knowledge of the cause of measles. The finding of green-producing cocci in the blood of early measles patients by Tunnicliff, Ferry, Cary and Day and others is interesting and important. Final judgment on the role of these organisms in the causation of measles must be withheld until unquestioned measles has been produced by them in man or in experimental animals.

SUSCEPTIBILITY AND IMMUNITY.

Susceptibility to measles is *practically universal*. All mankind, almost without exception, will take the disease when exposed to it. The temporary insusceptibility exhibited by very young infants will be referred to later.

One of the most remarkable and instructive epidemics of measles in history is that which visited the Faroe Islands in 1846.[1] These

[1] This remarkable epidemic was carefully studied and reported by Panum, who visited seventeen of the twenty islands of the group during a period of four months. A later epidemic in 1875 was assiduously investigated by E. M. Hoff (Sundhedscollegiets Aarsberetning for 1876).

islands had been free from measles since 1781, a period of sixty-five years. The disease was introduced by a Danish cabinet-maker, who had become infected in Copenhagen. On his arrival at Thorshavn, the chief port of the islands, he communicated the disease to two friends. These persons gave rise to an epidemic which in a short space of time attacked over 6000 subjects out of a population of 7782. Persons of all ages were stricken and almost every household was converted into a hospital. The old inhabitants who had passed through an attack as children in 1781 alone escaped. Not one old person who was exposed to the infection, and was unprotected by previous attack, failed to take the disease.

That certain individuals may exhibit a *temporary immunity* against measles is recognized by most writers. Thomas says: "I observed, during an epidemic among about 130 cases, 5 children, 2 of whom were boys of two and three years, evince an immunity during this epidemic, while 2, boys of eight and twelve years, and a girl of nine years, had evinced it as well during previous ones."

Hoff makes mention of 3 men, acting as nurses in the epidemic of 1846 in the Faroe Islands, who remained exempt, but who contracted the disease when it recurred in the islands in 1875.

Spiess[1] states that a number of children, varying in age from four to seventeen years, after having been previously exposed to measles without contracting it, fell ill in 2 cases after seven weeks, in 1 after two months, in 4 after two and a half months and in 1 after five months.

Moore[2] reports the case of a boy who, passing through two epidemics of measles with impunity, fell ill during a third and gave the disease to a younger brother, who at the time of the first invasion was not born, but who had successfully resisted the second one.

It is difficult to explain this temporarily absent susceptibility, but it is quite analogous to that observed in suckling infants.

The presence of an acute disease is apt to temporarily diminish susceptibility to measles, or, when the infection is received, to postpone its outbreak until convalescence from the first disease. This is true of most of the exanthematous affections. The susceptibility to measles may even be temporarily abolished during the existence of another acute malady.

Skin Tests in Measles.—Tunnicliff[3] states that skin tests conducted with anaërobic dextrose broth cultures of her green-producing diplococcus found in measles, killed by 0.5 per cent phenol, appeared to produce a reaction in persons who had not had measles; Tunnicliff and Taylor[4] subsequently reported positive skin reactions in 100 per cent of individuals who had never had measles following the intracutaneous injection of the soluble toxin of this organism. Only 4 per cent posi-

[1] Quoted by Thomas: Loc. cit.
[2] Ibid.
[3] Jour. Infect Dis., 1925, **37**, 193.
[4] Jour. Am. Med. Assn., 1927, **87**, 846.

tive reactions are said to have been observed in individuals who have had the disease.

Ferry and Fisher[1] have also reported positive skin reactions with the toxin of their streptococcus; Musser[2] has likewise observed positive reactions and believes that this diplococcus-streptococcus of Tunnicliff and Ferry is the specific cause of the disease. But this work awaits further corroboration before a final opinion can be expressed.

Age.—Measles most commonly attacks individuals between the ages of one and ten years. This age incidence is determined by several factors—an almost universal vulnerability to the disease, a diminished susceptibility during the first year of life and the immunity conferred by one attack. There can be no doubt that infants under one year of age and particularly those under six months will commonly escape measles when exposed to the disease. This is equally true of rubella and, in a measure, true also of scarlet fever. This immunity is not absolute, but only relative. There are numerous records of infants of tender age who have contracted measles, but under six months they are very apt to resist the infection altogether.

Pfeilsticker[3] reports an interesting epidemic of measles occurring in Hagelloch, near Tübingen, in which 188 out of 197 children under fourteen years of age, contracted the disease. Seven of the children were under six months of age and *all of this number remained well.* Of 10 infants between six months and one year, 9 contracted measles. This experience would tend to show that infants under six months of age are very much more immune than those a few months older.

Le Barbillier,[4] in an epidemic of measles in the Foundling Hospital at Bordeaux, noted but 7 cases among 40 children under one year of age. Mayr reports that of 10 new-born and suckling infants exposed to the disease, but 1 contracted it.

Herrman[5] states that infants under two months of age whose mothers have had measles are immune; the immunity becomes less marked as they grow older, but that even at four or five months of age only 25 per cent are infected. From that time the relative immunity quickly diminishes, so that infants over nine months of age are as susceptible as older children. Debre and Joannon[6] have expressed a similar opinion.

The susceptibility, then, to measles is largely in abeyance during the first six months of life; after this period it gradually increases so that after the first year the temporary immunity has entirely vanished.

Measles may in extremely rare cases be contracted during intrauterine existence, and children may be born with fully developed eruptions. After careful search of the literature Thomas was able to find

[1] Jour. Am. Med. Assn., 1926, **86**, 932.
[2] Proc. Soc. Exper. Biol. and Med., 1927, **24**, 518.
[3] Beiträge zur Pathologie der Masern, etc., Tübingen, 1863.
[4] Quoted by Thomas: Loc. cit.
[5] New York State Jour. Med., 1923, **23**, 404.
[6] Bull. Med., 1925, **39**, 111.

but 6 properly authenticated instances of this occurrence. Numerous authors refer to congenital measles, but the facts in many cases render the diagnosis doubtful. Several authors cited by Thomas record cases which bear the stamp of genuineness. Clarus reported to the Medical Society of Leipzig that he had seen the eruption of measles quite plainly on the fetus, the mother of which had died during the exfoliative stage of the disease. Hedrich speaks of a female child born on the fourth day of an attack of measles in the mother that was covered with the measles exanthem and had catarrhal symptoms, sneezing, coughing and inflamed eyelids. Vogel, Guersent, Hildanus, Lidelius, Michaelson, Seidle, Ballantyne and others have also reported cases which in all number about 20. The diagnosis in such cases could be controlled, as Thomas suggests, by noting the susceptibility or immunity of these children in later years. He reports an attack of measles in a woman five months pregnant, in which the susceptibility of the fetus was not affected, for the child contracted measles at the age of nine years.

Von Jürgensen says: "The poison must be able to pass through the placenta. It is presumed that the child becomes infected very soon after the disease organisms have attacked the mother, since the disease presents the same stage of development in mother and child at the time of the latter's birth."

Hoff, on the other hand, states that "Without exception, everybody born in the year 1846 whose mother, according to her own statement and as affirmed by comparison with the church records, contracted measles during pregnancy, was attacked by the disease, if exposed to it, at the time of the epidemic of 1875." Hoff states that this was true no matter what month of pregnancy the mother happened to be in when she was suffering from the measles. This experience throws a flood of light upon the question of the placental transmission of measles. Hoff draws therefrom the conclusion that "There is not the slightest ground for believing the contagion to be carried to the fetus through the placental circulation."

Adult life offers no such immunity against measles as is commonly observed toward scarlet fever. Those who escape measles in childhood do not fail to take the disease when exposed in later years. Measles in adults is comparatively uncommon only because most persons have suffered an attack in childhood. Gregory states that measles was absent from the island of Madeira for twenty-five years; when, in 1808, it did invade the island it found almost the whole population susceptible, and in four months destroyed 700 lives.

Panum states that in the epidemic of measles in the Faroe Island, in 1846, not one person who had escaped measles in the epidemic of 1791 remained free of the disease. It is evident that all of these persons must have been over fifty years of age. Measles may even attack persons in the decrepitude of old age. Drake,[1] in 1844, observed

[1] Drake, Heim and Michaelson, all cited by Thomas (Loc. cit., p. 48).

several cases in negroes of advanced age, one of them at least eighty years of age. Heim saw a woman, aged seventy-six years, with measles, and Michaelson reports a case in a patient aged eighty-three years.

Measles is undoubtedly the most common of all of the exanthematous diseases. Owing to its extremely contagious character epidemics are far more extensive and widespread than those of scarlet fever. While large cities are subject to epidemic outbreaks from time to time, the disease seldom dies out altogether. In great centers of population the disease may be said to be endemic, sporadic cases developing every now and then. When the increase in population by births or other causes creates a sufficient number of unprotected subjects the infection takes hold and an epidemic results. Thomas asserts that in large communities epidemics may be expected about every two or four years. In small towns and villages the interval of freedom is much longer.

Whitelegge,[1] from a careful study of English statistics, estimates that epidemics of measles appear about every two years. About every ten years an epidemic of considerable severity with high death-rate may be expected.

Measles may from time to time cover so extensive a territory as to become *pandemic*, in the same manner as smallpox, particularly before the days of vaccination. At such times an entire country, or, indeed, several countries may be attacked. Hirsch mentions a number of such general outbreaks during the century just passed. In 1796–1801 measles was present in a large part of England and France; in 1823–1824 it prevailed extensively in Germany, and in 1826–1828 in the Netherlands and Germany. In the two years from 1834 to 1836 it swept over the greater part of northern and middle Europe. An extensive epidemic prevailed in 1846–1847 in both the new and the old hemispheres. Since the days of rapid transoceanic travel it is quite easy for diseases like measles and smallpox to be contracted on one side of the ocean and to develop on the other. Infectious diseases follow the channels of travel. Measles is not apt to be carried by infected baggage or clothing, but by the breeding disease in an exposed and unprotected person.

Season.—According to Gregory it was formerly believed that measles began in January, reached its crisis at the vernal equinox and ceased in the summer solstice. Gregory dissents from this view and states that "The recurrence and duration of epidemics are in Europe wholly irrespective of season. In Bengal, however, measles never originates except in the cold season. Season affects, too, there the character of the symptoms. In the hot months the eruption is more vivid and more elevated, and the internal organs comparatively but little affected. In the cold season the affection of the mucous tissues is best developed."

[1] Brit. Med. Jour., 1893, i, 541.

Hirsch's figures show that, while measles most commonly occurs during the winter months, no season of the year is entirely exempt.

Three hundred and nine epidemics collated by Hirsch began in the following months:

THREE HUNDRED AND NINE EPIDEMICS OF MEASLES CLASSIFIED ACCORDING TO SEASON (HIRSCH).

December	28	June	19
January	54	July	16
February	14	August	8
Winter, 96 epidemics		Summer, 43 epidemics	
March	43	September	16
April	28	October	34
May	23	November	26
Spring, 94 epidemics		Autumn, 76 epidemics	

Thomas suggests that the lessened incidence of measles in mild weather may be, in part, due to the better ventilation of sick-chambers and the consequent diminished concentration of the infection. In cities a much more important cause of the falling off of measles in hot weather is the closing of the schools. All of the exanthematous diseases in large communities diminish during the school vacations and increase upon resumption of the sessions in the fall. There can be no doubt that the close contact of children in the schools is a fertile cause of the spread of the various contagious diseases.

Contagious Period.—The contagious period of measles may, in general terms, be said to last from the beginning of the prodromal stage to the complete disappearance of the eruption. That measles can be communicated before the appearance of the eruption is generally admitted by writers, and is borne out by observation.

Panum[1] details the history of a case in the Faroe Islands in which a young man had slept in a bed with an infected patient "several days" before the rash broke out; fourteen days later the eruption of measles appeared upon him. Hoff reports an equally conclusive instance in the case of a clerk infected at Thorshavn.

Eyre[2] reports an interesting and apparently conclusive instance of preëruptive contagion. A schoolmaster at Beckenham returned to his school on April 30, 1888, at the end of the Easter holidays; he did not feel well, but continued his work on May 1 and 2. He went to bed on the evening of May 2, and during the night the eruption appeared. Although the students were sent away, all of the susceptible ones—14 in number—contracted the disease.

Ransom[3] collected 5 instances of measles infection conveyed before the appearance of the rash. In 2 of these cases the disease was communicated two days before the eruption. In a case seen by Croskey[4]

[1] Virchow's Arch. f. path. Anat., vol. 1, p. 499.
[2] Brit. Med. Jour., February 23, 1899.
[3] Ibid., January, 1877.
[4] Quoted by Ransom: Loc. cit.

the infection was believed to have been transmitted four days before the appearance of the rash. Holt reports a similar case occurring in in the Babies' Hospital in which the disease was conveyed four days before the eruption appeared. On the other hand, one of Ransom's cases failed to give the disease to 7 susceptible children exposed three days before the eruption appeared.

Measles is *most contagious* at the height of the eruption. Indeed, some writers contend that the communication of contagion is limited to the eruptive stage. This is the opinion of Hoff, who had a splendid opportunity of studying the Faroe Islands cases. Panum says it is uncertain whether the catarrhal and desquamative stages are contagious. Peterson, a colleague of Hoff, concedes that the catarrhal period may be contagious, but denies that this extends to the stage of desquamation.

We have on several occasion had children brought into the wards of the Philadelphia Hospital for Contagious Diseases with the stains of the measles exanthem still visible; although in each of these instances a score of children were freely exposed, many of whom were unprotected by previous attack, no cases of measles developed among them.

There can be no doubt that the contagiousness of measles is distinctly diminished during the stage of desquamation. We would be extremely loath to assert, however, that it is abolished at this time, and we would certainly not act upon the assumption that it is. In the absence of adequate and conclusive data upon this point it is advisable to isolate measles patients until the completion of desquamation, or, at any rate, for a period of three weeks from the commencement of the disease.

Second Attacks.—One attack of measles nearly always confers immunity against subsequent attacks. It is generally admitted by careful and experienced observers that second attacks are extremely rare. The infrequency of this occurrence may be appreciated when it is stated that Maizelis[1] was able to find only 106 instances of multiple attacks in the entire literature of the subject. Of these, 103 were second attacks and 3 were alleged to be third attacks. This is an exceedingly small number, even admitting many unpublished cases, when the universal extent of measles is considered.

Panum, who saw 6000 cases in persons of all ages in the Faroe Islands epidemic, did not observe one instance of second attack. Rosenstein, in an experience extending over forty years, met with but a single instance of the recurrence of measles. Willan, in a rich experience of twenty years, did not see one case. Camby could not recall one instance of relapse or recurrence among 700 cases of measles. Thomas's large experience did not include a case and the same may be said of the authorities quoted by him—Berndt, Theussink, Schönlein, Mayr, Schott and Bartscher. While the experience of these eminent physi-

[1] Ueber die durch das Ueberstehen von Infectionskrankheiten Immünität, Virchow's Arch. f. path. Anat., vol. **137**, p. 468.

cians indicates the great infrequency of second attacks, a sufficient number of cases has been reported to prove their occasional occurrence.

Recurrences may take place a few days to a few weeks after the first attack, in which event one might properly speak of a *relapse*, or they may take place months or years later, constituting true *second* attacks. Relapses have been reported by a considerable number of observers.[1]

The relapses commonly occur from two to four weeks after the first attack. Thomas believes most of these cases to be due to auto-infection similar to the relapses of typhoid fever. Lippe, who saw 15 relapses in three epidemics, claims that the children contracted the second attack three or four weeks after the first, from contact with another case of measles. In quite a number of reported cases the relapse has developed immediately after the completion of the course of the original attack. It is not uncommon for the second attack to be inversely proportionate in gravity to the severity of the first. Seidl[2] reports 3 malignant recurrences, 2 of which ended fatally.

Second attacks proper may occur from two or three months to twenty years or more after the first illness. Gregory states that Dr. Baillie reported 7 instances of recurring measles, 5 of which occurred in one family; 4 had second attacks after an interval of six months and 1 at the end of twenty-one years. Webster[3] published 3 cases in which the intervals were two, four and six years respectively.

The list of reported instances is quite a long one and includes cases published by most reliable writers.

Several apparently authentic instances of *third attacks* of measles are on record. Van Diezen,[4] of Antwerp, published an account of three successive attacks in a child three years of age. The first attack occurred early in February, the second on March 4 and the third on April 12. The attacks were well marked, the last being preceded by vomiting and convulsions. All were followed by a branny desquamation. Hennig[5] relates having attended a woman during two attacks of measles at the age of thirty-two and thirty-three years respectively, who had had in all probability an attack at the age of thirteen years. Cases have also been reported by Drysen, Bierbaum, Spiess, Home and Streng, although Thomas is of the opinion that the facts in the most of these cases are not entirely convincing. The probabilities are that many cases of alleged multiple attacks have represented an error of diagnosis in one of the illnesses.

Starck[6] has recently reported 2 cases of alleged reinfection, but Loos[7]

[1] Among those who have reported relapses of measles may be mentioned Van Diezen, Battersey, Robédière, Flemming, de Haen, Haartman, Webster, Kassowitz, Stiebel, Brunzlow, Luithlen, Mauthner, Kierulf, Trojanowsky, Home, Lewin, Gauster, Karg, Bèhier, Tresling, Spiess, Feltz, Lemoine, Vergeley, Fischer, Roger and others.

[2] Cited by Thomas: Loc. cit.

[3] Med. Chir. Trans., vol. **22**, p. 245.

[4] Bull. gén. de thérap., September 15, 1848, p. 239.

[5] Exanthematica, Jahrb. f. Kinderh., vol. **8**, p. 417.

[6] Wien. klin. Wchnschr., 1924, **37**, 1325.

[7] Ibid., 981.

does not believe this is possible and is of the opinion that rubella may be confused with it.

The eruption of measles may at times be so closely simulated by that of rubella that an error may very readily be made. Histories given by patients are not authentic in determining the character of an illness long past. The experience of such men as Willan, Panum, Rosenstein and Thomas, which is in accord with that of most of the careful observers, teaches that second attacks of measles are exceedingly rare.

THE SYMPTOMATOLOGY OF MEASLES.

Incubation Period.—The incubation stage of measles may be said to be the period elapsing between the date of infection, which, in most cases, is the time of initial exposure and the development of febrile symptoms. In the majority of cases this stage is in the neighborhood of ten days; the eruption usually appears on or about the fourteenth day. It is only possible to accurately determine the duration of the incubation stage in cases in which the exposure has been but once and for a brief period.

While persons susceptible to measles will ordinarily take the disease upon first contact, this is not invariably the case. Where there has been prolonged exposure it is not possible to accurately fix the time of infection.

Some writers speak of the incubation period of measles as about fourteen days. In such a statement there is either an inaccuracy of time or terms. The incubation period ceases when the usual symptoms of measles manifest themselves. While there is a decided variability in the duration of the symptoms preceding the eruption, we are not justified in speaking of the incubation period as extending to the appearance of the eruption.

In general terms it may be said that the incubation stage of measles is about *ten or eleven* days. The period from exposure to the development of the rash is about fourteen days. The incubation period in this disease is subject to less variation than in scarlet fever, rubella, or chickenpox. Panum had a splendid opportunity of studying the incubation period in the Faroe Islands epidemic. He reports about 40 cases, in all of which the period to the appearance of the rash was thirteen or fourteen days. The facts in these cases are thoroughly reliable, the date of exposure having been accurately determined in each. Smith and Dabney[1] report an outbreak of measles in an institution in Virginia, in which the disease developed in 20 children just eleven days after the rash appeared in the first patient. Spiess[2] estimated the time elapsing between the appearance of eruptions in the infecting and infected patients in 147 cases. In 117 cases the interval was between ten and fourteen days, in 8 cases it was nine

[1] Quoted by Holt: Loc. cit.

[2] Cited by Thomas: Loc. cit.

days and in 22 cases it was between fifteen and eighteen days. Salzman[1] found the interval between the eruptions in 25 cases infected from a single patient to be as follows: In 3 cases it was nine days, in 8 cases ten days, in 13 cases eleven days and in 1 case twelve days.

Holt[2] collected a series of 144 cases, of which 25 were his own, in which the incubation period could be traced definitely. The periods were as follows: Incubation of less than nine days, 3 cases; incubation of nine or ten days, 22 cases; incubation of eleven to fourteen days, 15 cases; incubation of fifteen to seventeen days, 19 cases; incubation of eighteen to twenty days, 5 cases.

In 66 per cent of the cases the incubation was between eleven and fourteen days, and in but 1 case was it under a week. There have been cases in which the incubation period has been but five days, but such instances must be exceedingly rare. On the other hand, unusually long periods are on record. Roux[3] observed an epidemic of measles that developed among a number of people on shipboard after the vessel was seventeen days out of port; no case of measles had previously existed among those on board.

While it is seen that some variability exists in the incubation period of measles, it will be found in the majority of cases to be in the neighborhood of ten or eleven days.

While the incubation stage is generally devoid of symptoms, patients occasionally feel unwell and complain of lassitude, headache, malaise, etc., during the latter part of the period. Gregory says: "Sometimes the entire incubation stage is marked by languor, lassitude and a sense of malaise and occasionally a characteristic symptom, such as cough."

Prodromal or Invasive Period.—In those cases in which the latter days of the incubation period are marked by mild constitutional disturbances the invasive stage comes on insidiously. It is rather uncommon for measles to be ushered in abruptly with high fever. The onset is more gradual and characterized by less intensity than that of scarlet fever. Convulsions and vomiting are rare occurrences. The mucous membranes are early attacked, giving rise to symptoms which have caused this period to be known as the catarrhal stage. The eyes are reddened and watery, sensitive to light and often show puffiness of the lids. The nose at first feels obstructed, but soon a discharge issues therefrom, accompanied by repeated sneezing. Occasionally nose-bleed occurs, but this is seldom severe. In pronounced cases the face may present a puffy and swollen appearance. The involvement of the larynx and trachea gives rise to hoarseness and to a dry, hard and high-pitched cough. At times the throat is sore, exhibiting upon inspection redness and swelling of the tonsils, soft palate and pharynx. The constitutional symptoms consist of fever, headache, loss of appetitie, drowsiness and irritability. Somnolence

[1] Cited by Thomas: Loc. cit
[2] Diseases of Infancy and Childhood, New York, 1899, p. 911.
[3] Quoted by Thomas: Loc. cit.

is often a prominent feature. Chills are rare, occurring, according to Ziemssen and Krabler, only 5 times in 311 cases studied by them. The bowels are usually constipated, although occasionally a slight diarrhea is observed.

The *fever* does not observe any set standard, but is subject to considerable variation. In some cases it rises rapidly during the first twenty-four hours reaching by evening 102° to 103° F. On the

Fig. 105.—Patient with measles exhibiting eruption and catarrhal inflammation of the eyes.

morning of the second day, or occasionally the third, the temperature may decline to normal or thereabouts, accompanied by an improvement in all of the symptoms. After this remission the temperature again begins to rise, usually on the evening of the third day, continuing its ascent on the fourth day, with the appearance of the eruption. In other cases the fever is very moderate at the outset, not exceeding 101° F. A gradual increase in the temperature and in the

catarrhal symptoms occurs up to the appearance of the rash. In some epidemics the prodromal symptoms are so mild as to escape the observation of the parents of the patient, who then assert the eruption to be the first symptom. On the other hand, there are epidemics in which measles develops abruptly with high fever in such a manner as to disguise the oncoming disease until the appearance of the rash solves the diagnosis.

In the average case of measles the invasive period lasts about four days; there are, however, numerous exceptions to this duration, particularly in infants. Holt made notes of the duration of the invasive stage in 270 cases His figures are appended:

	Cases.		Cases.
One day or less	35	Six days	20
Two days	47	Seven days	6
Three days	64	Eight days	2
Four days	64	Nine days	2
Five days	29	Ten days	1

Enanthem, or Mucous-membrane Eruption.—It is a proved observation that the eruption of measles may be seen on the mucous membrane of the mouth in advance of its appearance on the cutaneous surface. Commonly, on the second day, inspection of the mouth will disclose the presence of an enanthem. The presence of a mucous-membrane eruption was recognized by physicians in the early part of the nineteenth century, as is evidenced by the writings of Willan, Heim and others. Most of these and later observers have described the enanthem as consisting of dark-red or light-red spots.

Flindt,[1] in 1880, described the enanthem of measles in a most accurate and detailed manner. He says: "The eruption consists of round or somewhat irregularly-shaped, light-red spots, not very distinctly circumscribed, and only just raised above the level of the mucous surface. The spots vary in size from a pin-head to a lentil, are in part isolated and in part collected into groups, quite irregular in shape and in some places coalescent. At the center of the small red spots, and giving them a peculiar appearance, are situated numbers of tiny, whitish, shiny, raised points, apparently vesicular in character and irregularly grouped according to the arrangement of the spots on which they lie. These tiny miliary vesicles can be both seen and felt as distinct elevations. The palpebral conjunctiva is reddened throughout, and besides the net-like injection dependent on the distribution of its blood supply it sometimes appears spotted and covered with miliary, pearl-covered, raised points, similar to those on the mucous membrane of the palate.

"Similar groups of spots and vesicles can now also be perceived on the mucous membrane of the cheeks, especially on the parts corresponding to the space between the upper and lower molar teeth."

[1] Reports of the Danish Board of Health, translated and cited by von Jürgensens.

The measles enanthem was carefully studied by Filatow (1895), Canby (1895) and Koplik (1896). The last-named physician[1] describes the mucous-membrane eruption as follows: "If we look in the mouth at this period (invasion) we see a redness of the fauces; perhaps, not in all cases, a few spots on the soft palate. On the buccal mucous membrane and inside of the lips we invariably see a distinct eruption which consists of small, irregular spots of a bright-red color. *In the center of each spot* there is noted, in strong daylight, a *minute, bluish-*

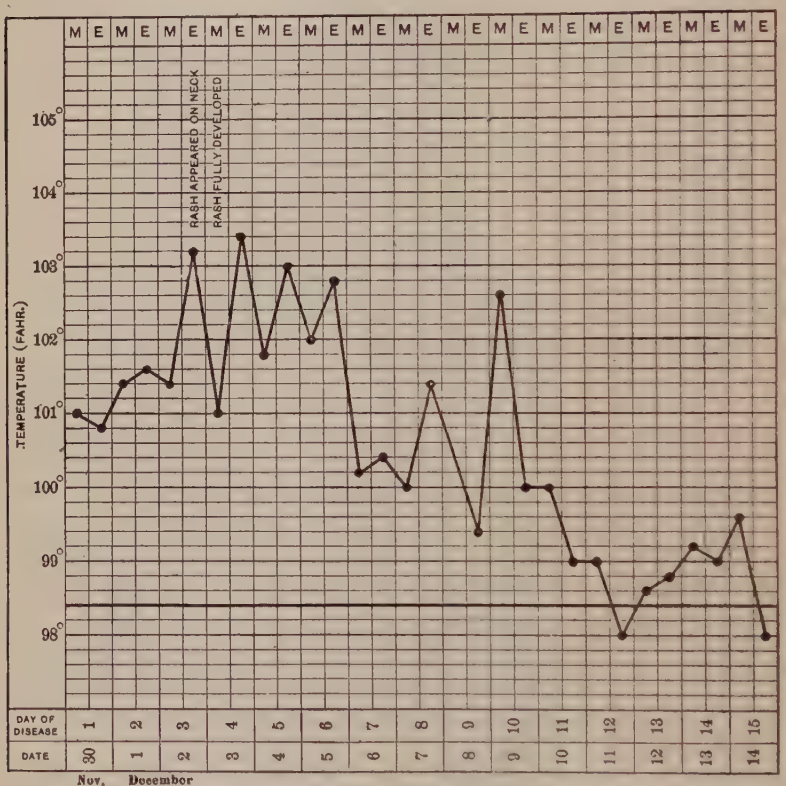

M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E
105°
104°
103°
102°
101°
100°
99°
98°
TEMPERATURE (FAHR.)
RASH APPEARED ON NECK
RASH FULLY DEVELOPED
DAY OF DISEASE
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
DATE
30 1 2 3 4 5 6 7 8 9 10 11 12 13 14
Nov. December

FIG. 106.—A case of measles in a child, aged three and a half years, developing in the Philadelphia Hospital for Contagious Diseases; temperature record from the first day of illness.

white speck. These red spots with accompanying specks of a bluish-white color are absolutely pathognomonic of beginning measles, and when seen can be relied upon as a forerunner of the eruption. No one has to my knowledge called attention to the pathognomonic nature of these small, bluish-white spots. Sometimes only a few red spots with this central bluish point may exist—six or more; in marked cases they may cover the whole inside of the buccal mucous membrane.

[1] Arch. Pediat., December, 1896, vol. **13**; Med. Rec., 1898.

PLATE XVIII

FIG. 1

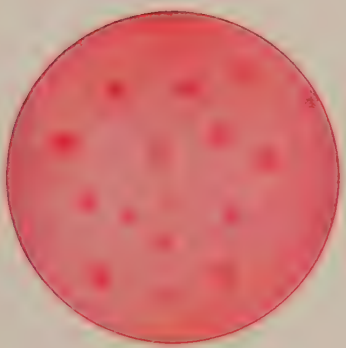


FIG. 2

FIG. 3

FIG. 4

The Pathognomonic Sign of Measles (Koplik's Spots).

FIG. 1.—The discrete measles spots on the buccal or labial mucous membrane, showing the isolated rose-red spot, with the minute bluish-white center, on the normally colored mucous membrane.

FIG. 2.—Shows the partially diffuse eruption on the mucous membrane of the cheeks and lips; patches of pale pink interspersed among rose-red patches, the latter showing numerous pale bluish-white spots.

FIG. 3.—The appearance of the buccal or labial mucous membrane when the measles spots completely coalesce and give a diffuse redness, with the myriads of bluish-white specks. The exanthema on the skin is at this time generally fully developed.

FIG. 4.—Aphthous stomatitis apt to be mistaken for measles spots. Mucous membrane normal in hue. Minute *yellow points* are surrounded by a red area. Always discrete. (Hare.)

"The eruption just described is of greatest value at the very outset of the disease, the invasion. As the skin eruption begins to appear and spreads, the eruption on the mucous membrane becomes diffuse and the characters of a discrete eruption disappear and lose themselves in an intense general redness. When the skin eruption is at the efflorescence the eruption on the buccal mucous membrane has lost the character of a discrete spotting and has become a diffuse red background, with innumerable bluish-white specks scattered on its surface. The mucous membrane retrogrades to the normal appearance long before the eruption on the skin has disappeared."

Koplik also speaks of irregularly-shaped, rose-colored spots and streaks which are commonly seen on the hard and soft palate and also on the cheeks. They present small, whitish, punctate, miliary vesicles. Koplik states that the rose-colored papules or streaks with superimposed miliary vesicles are found in rötheln, scarlet fever and some cases of simple angina, but the reddish spots with bluish-white specks in their centers occur only in measles.

Subsequent observations have confirmed the claims as to the pathognomonic nature of these spots. They do not appear to be present in any other disease. We have examined the mouth in many cases of rubella and have noted the presence of red spots similar in appearance to those seen on the skin, but we have never seen such spots surmounted by bluish-white specks as occur in measles.

Filatow speaks of a desquamation of the epithelium of the mucous membrane of the lips and cheeks in the form of whitish shreds.

Baginsky noted desquamation on the gums in the form of whitish patches and thought this appearance to be characteristic of measles. We have repeatedly noted the presence of these whitish patches on the gums in scarlet fever.

The presence of the measles enanthem is of great diagnostic value; its absence has a less important negative evidence because in a small proportion of measles cases the spots are not present. We have seen a small proportion of cases of measles in which the Koplik spots were absent. Of 187 cases of measles examined by Cotter[1] at the New York Foundling Hospital 169 showed the characteristic spots. In 8 patients the spots were absent, while in 10 patients their presence was doubtful. In 78 cases the spots appeared synchronously with the cutaneous eruption; in 88 cases the spots preceded the eruption by one to five days; in 2 cases the spots did not appear until after the rash.

Lorand[2] studied the incidence of Koplik's spots in two series of cases of measles, numbering in all 523. The spots were absent in 30 cases out of this number.

Preëruptive Rashes in Measles.—In almost all of the exanthematous fevers the true specific eruptions may be preceded by accidental

[1] Arch. Pediat., 1900, vol. **17**.
[2] Jahrb. f. Kinderh., 1901, **3**, 658.

rashes. Measles is no exception, although prodromal erythemata in this disease are rare.

Meredith Richards[1] says: "In the preëruptive stage of measles there may be a scarlatiniform rash, usually more transient and more diffuse than the eruption of scarlatina. This rash is responsible for some of the cases in which measles is diagnosed as scarlet fever. Another preeruptive accidental rash is a somewhat faint general erythema, not unlike the true measles eruption in its general appearance, but almost confined to the trunk and limbs and more diffuse and less distinctly papular.

Roger[2] records 5 cases of prerubeolic erythema occurring among 1917 cases of measles. These developed in an infant fourteen months of age, a child three years of age and three adults, and appeared two or three days before the time of the measles eruption. We recall a young girl, aged fourteen years, in whom a partial scarlatiniform erythema of considerable intensity developed upon the neck, face and upper part of the chest on the second day of the febrile symptoms. The symptoms suggested at first an atypical scarlatina. The rash disappeared, however, in about thirty-six hours, and twelve hours later, on the fourth day of the illness, the eruption of measles appeared. Gerhardt[3] observed a prodromal exanthem in the femoral triangle which appeared a day before the measles eruption. Comby[4] records 2 cases of preëruptive rashes. A girl, aged four and a half years, developed at the beginning of the invasive stage of measles a scarlatiniform eruption which persisted throughout July 18 and 19, the true measles exanthem appearing on July 22d. Another child of the same age was admitted to the hospital on July 20th with a morbilliform rash; On July 22d the measles eruption appeared.

The cause of these accidental rashes cannot be readily assigned. In most of Roger's cases the rashes were morbilliform; it is possible that these represent abortive attempts of the true eruption to appear before the usual time. Thomas says: "The earliest signs of the eruption, at first in a thoroughly undeveloped condition, appear not infrequently upon the first day of the febrile period, more often on the second or third." The scarlatiniform rash, whatever may be the cause, is of importance because of errors of diagnosis which its presence may occasion.

The Eruptive Period.—The measles exanthem usually appears upon the fourth day of the febrile disorder. It does not invariably appear in one particular locality, as some writers state. The most common initial sites are the side of neck, the mastoid region of the temples and frontal border of hair, the cheeks and the chin—in other words, about the face and neck. The eruption of measles has a special predilection

[1] Accidental Rashes Occurring in the Course of the Exanthemata, Quart. Med. Jour., 1898, 5, 31.

[2] Les maladies infectieuses, Paris, 1902, p. 874.

[3] Quoted by Thomas.

[4] Traité des maladies d'enfance, Paris, 1897.

for the face, which is earlier and more copiously covered than other areas.

It is not uncommon for the eruption in this region to become confluent and to give rise to a dusky turgescence of the skin. From the face and neck the rash rapidly extends over the trunk and upper extremities. The lower extremities are the last and least intensely attacked; commonly but a few scattered lesions are seen upon the legs.

Aitken[1] describes the measles eruption as appearing in three crops. The first crop appears on the face, neck and upper extremities, on the third or fourth day of the disease; on the following day the second crop covers the trunk and on the third day the third crop appears on the lower extremities.

Character of the Eruption.—The essential lesion of measles is a slightly elevated macule; it is sufficiently elevated to be recognized both by the sense of sight and touch. The more circumscribed the lesion is, the more is it distinctly papular, and the more diffuse and confluent the eruption is, the more does it approach an erythematous and unelevated efflorescence. The macules vary greatly in size from a pinhead to a bean or finger-nail. They are irregular in outline, being at times rounded or oval, but at other times angular, indented and spun out. They are usually sharply marginated and stand out sharply against the pale, integumentary background.

FIG. 107.—Measles exanthem on the third day of the eruption and the seventh day of the disease.

To the finger passed over the lesions a soft or velvety feel is imparted, quite unlike the indurated feel of the early smallpox eruption. The color of the measles exanthem varies in different patients and at different stages in the same individual. It is seldom as vivid a red as is seen in the exanthem of scarlatina. The macules in the beginning have

[1] The Science and Practice of Medicine, 1868, p. 288.

commonly been compared with the appearance of flea-bites; they are of a dull-red color, not infrequently becoming dusky. In some patients the eruption, particularly when it becomes confluent, has a distinct bluish tinge. The bluish coloration is not at all uncommon upon dependent areas, such as the back. In pronounced cases, particularly in adults, the face may exhibit an extremely dusky-red appearance, which, with a slight swelling of the skin, produces a strange and disfiguring turgescence.

On the first day of the eruption the lesions are small and discrete, in many cases bearing a resemblance to the eruption of rubella. The macules subsequently enlarge in size and in number, coalesce in areas and produce a rash which is essentially blotchy. The arrangement of

Fig. 108.—Pronounced measles eruption on sixth day of the disease.

the measles lesions lacks symmetry and uniformity. At times distinct crescents and segments of circles can be distinguished; at other time such configurations are absent. The rash of measles does not invariably consist of slightly elevated, velvety macules. There are at times distinct papules present, and miliary vesicles are not infrequently seen.

Mayr, in his article on "Measles," in Hebra's *Diseases of the Skin* (1866), distinguishes a number of varieties of measles based upon the character of the eruption. The term *morbilli læves* is applied to the common form in which the character of the eruption is smooth and flat, the individual macules being separated by areas of healthy skin.

In *morbilli papulosi* there appear dark-red or reddish-brown points or papules, the size of millet or hemp seed, situated at the mouths of

hair follicles. This form of measles is said to occur in certain epidemics, taking the place of the more usual variety.

We have known the papular form to be confounded with smallpox on more than one occasion.

In *morbilli vesiculosi* or *miliares* small pin-point- to pin-head-sized vesicles are seen upon the summits of the lesions. This gives the skin an appearance resembling prickly heat, and, indeed, the presence of the miliary vesicles has been ascribed to the sweating process. This is probably not the case, as the vesicles are identical with those commonly seen in scarlet fever, in which disease the sweating process is in abeyance.

Morbilli confluentes describes the form in which the macules run together and become confluent. It will be remembered that this was the term applied to scarlatina before the days of Sydenham.

We have seen numerous cases which justify the use of the term confluent measles. We recall a very severe epidemic of measles which prevailed in the scarlet-fever wards of the Municipal Hospital some years ago. The eruption in these cases was normal in the beginning, but in a few days became intensely confluent and vivid over the greater part of the cutaneous surface. The resemblance of the rash after a few days to that of scarlet fever was striking, although in most every instance there could be found in one region or other, and commonly about the buttocks, pale areas of skin against which the marginate border of the confluent rash stood out in sharp contrast. The mortality among these patients was very high.

Morbilli hæmorrhagici is that variety in which the macules are purplish or bluish and from which the color cannot be made to disappear by the pressure of the fingers. This condition is usually observed in malignant cases.

The various lesions here described may be seen to a certain extent in ordinary cases, but the form characterized by papules, miliary vesicles or confluence may each be particularly well pronounced in certain epidemics.

As regards the rapidity of extension of the measles eruption, Thomas observes that if it appears early in the invasive stage it is apt to remain in a moderately developed condition for several days upon the face alone. A more rapid evolution and spread occur when the temperature begins to rise sharply. On the other hand, when the exanthem first appears at a late period, when the fever is reaching the acme, the rash spreads rapidly over the body. The intensity of the eruption and the degree of the fever increase *pari passu*. At the beginning of the eruption the temperature does not register its maximum; it is only after the full development of the exanthem that the pyrexial fastigium is reached. The temperature at this time is commonly 104° F., and not infrequently 105° F. The fever may reach even a higher degree than this. Temperatures of 108° and 109° F. have been observed, and Hunter[1] saw a child sixteen months of age with a temperature of

[1] Brit. Med. Jour., April, 1898.

110° F., the patient ultimately recovering. When the maximum fever is attained the eruption is copious and intense; the face is often of a uniform dusky-red color and edematous, particularly about the eyelids. The entire body is, as a rule, covered, not even the palms and soles being exempted. Not infrequently the rash gives rise to a considerable degree of itching.

Fig. 109.—Measles. Note conjunctival injection.

During the development of the eruption the local as well as the constitutional symptoms increase in intensity. The conjunctivæ are red and swollen and an abundant muco-purulent discharge issues from the palpebral cleft, later drying and gluing the lids shut. When the lids are open there is great sensitiveness to light. A similar profuse

discharge from the nose irritates and excoriates the nostrils and upper lip. There is commonly painful swallowing and enlargement of the glands at the angles of the jaw. The cough is frequent and harassing, and the voice hoarse and aphonic. Evidences of bronchitis are usually present at this time. The ear placed to the chest will discover the presence of dry and moist rales. In large children and adults there is expectoration of muco-purulent material. Children are much prostrated, manifest great thirst, refuse food and are either extremely restless and peevish or somnolent. Vomiting and abdominal pain are uncommon, but diarrhea is frequent, the stools being offensive and often slimy. The eruptive stage lasts ordinarily four or five days. With the fading of the rash there is a gradual subsidence of the fever and the catarrhal symptoms. It is rare for a critical fall of temperature with sweating to occur. When this does take place there is apt to be alarming prostration. The decline of the fever is by steps, but is nevertheless moderately rapid. Ordinarily but twenty-four to thirty-six hours elapse between the acme of the fever and the return to normal. When the decline is slower than this it is characterized by morning remissions and evening exacerbations. During convalescence the temperature may, for several days, be below the normal line.

As the rash fades the appetite improves, somnolence and irritability disappear, and the child begins to acquire its normal brightness and desires to leave the bed. The inflammation about the eyelids and the mucous discharges gradually improve, although the eyes may remain sensitive to light for some days. The hoarseness and cough persist for some time, but in favorable cases improve from day to day. Where no bronchial or pulmonary complications develop the patient is practically well at the end of ten days or two weeks, but, of course, requires to be carefully guarded against exposure.

Stains (Pigmentation).—As the rash disappears there are left on the skin faint reddish-brown stains which may be detected for a number of days. The stains correspond with the size and shape of the original lesions and are highly characteristic; they are of considerable diagnostic value, and will often enable one to diagnose an attack of measles after it has subsided. When children presenting the stains of the measles exanthem are admitted to a hospital or other institution they should be isolated in order that they do not transmit the disease to others. The stains may persist for a week or even longer.

Hemorrhagic Eruption in Measles of Moderate Severity.—It is not rare for the eruption in cases of measles of average severity to exhibit hemorrhagic extravasation into the skin. The macules in such cases are of a deeper hue, varying from a claret-red to a reddish-blue tint. It is observed that the spots do not disappear upon pressure of the fingers. The hemorrhage into the skin may be noticed at the height of the eruption, or it may become evident only during the decline, when the redness begins to fade. Claret-color or bluish discolorations are left, which pass through the color variations observed in an ordinary

bruise. The discolorations coincide in size and shape with the original measles spots.

It is important to distinguish this benign form of hemorrhagic eruption from the malignant variety. In the former the constitutional symptoms are not unusually severe and hemorrhages do not take place from the various mucous membranes. We have not infrequently noted hemorrhagic measles spots in cases of average severity, which pursued favorable course, terminating in recovery. Holt observed hemorrhagic eruptions in about 5 per cent of his cases.

Desquamation begins as the rash fades away and is first noted upon initial sites of the eruption, namely, the face and the neck. The scaling is branny and furfuraceous, and is often so fine as to require careful scrutiny to observe it. The skin seldom comes off in large flakes as it does in scarlet fever. The amount of desquamation varies in different cases and is usually proportionate to the intensity of the antecedent eruption. In many patients no desquamation will be seen at all. On the trunk the perspiration which is common in measles obscures the fine scales or enables them to cling to the body linen. The desquamation is usually most observable on the face. Scaling continues ordinarily from a few days to a week, but may rarely be protracted for ten days or two weeks.

Anomalous Cases of Measles.—All exanthematous diseases exhibit at times variations from what might be regarded as the normal standard. Anomalous cases of measles may develop individually during the course of a normal epidemic, or there may be special aberrant features peculiar to prevailing forms of the disease. The special predominance of the papular element of the eruption is more common in certain epidemics. Mayr says that the Nirlas or "Nirles of Alibert" was mostly probably a papular form of measles.

The chief deviations from the normal type are those forms that exhibit unusual benignity or exaggerated severity.

Mild Measles.—In rare cases there may be an absence of one or several of the important manifestations of the disease that go to make up the characteristic symptom-complex. Thus, measles may exist without fever, without catarrhal symptoms or, indeed, without an eruption.

Measles Without Fever (Morbilli Sine Febre), Morbilli Apyretica.—Leube says: "Although there may be very little fever in mild cases, it is never entirely absent." Nevertheless, von Jürgensen[1] reports 2 cases of measles occurring in infants of four weeks and twenty-one months of age, respectively, who had catarrhal symptoms and undoubted eruptions, and who had been exposed to measles, who never had any elevation beyond 99° F. Extremely mild and abortive cases of measles appear to be more common in young infants, who, as has been stated, possess only a very limited susceptibility to the disease.

Measles Without Catarrhal Symptoms (Morbilli Sine Catarrho).—The absence of catarrhal symptoms is occasionally noted in infants during

[1] Loc. cit., p. 267.

the prevalence of measles of the ordinary type. In such cases there is usually very little elevation of temperature and the eruption is not intense. The genuineness of these attacks is established not only by previous exposure to regular measles, but by the immunity conferred against subsequent attacks. It is evident that when the fever and catarrhal symptoms are insignificant the case must present considerable resemblance to rubella. If a disease prevails epidemically, in which these two groups of symptoms are uniformly in abeyance, the strong probabilities are that the disease is rubella and not measles.

Measles Without Eruption (Morbilli Sine Exanthemate, Morbilli Sine Morbillis).—As is the case in smallpox and scarlet fever, it is possible for measles to occur without the development of the exanthem. Such cases are, of course, excessively rare, but are recognized by careful and conservative writers. Thomas says that the diagnosis is more often made than is justified, but remarks that "This form of the disease may be diagnosed in persons previously unattacked, if in a single case, during an epidemic of measles, the characteristic mucous-membrane symptoms together with fever appear and become exactly as much developed as in measles with an exanthem, so that we have ground for assuming that this symptom alone is lacking from a normal course." Cases may occur in which the attack of measles is typical up to the eruptive stage, but at this point the anticipated exanthem fails to appear and convalescence is established. Embden[1] claims to have observed 20 patients among 461 cases of measles in Heidelberg, in whom the eruption was absent. The cases were of a mild type, but some few had severe complications.

Rush makes mention of persons who in 1789 presented the usual manifestations of measles, fever, cough, etc., but no eruption except in some cases a trifling efflorescence about the neck and breast. Webster[2] claims to have seen similar cases in 1773 and 1783.

Well-authenticated cases of this kind are said to have been seen in an epidemic in Paris in 1850. The usual premonitory symptoms of measles appeared in a number of children; the regular course was followed in a certain proportion, but in a number of others some presenting unequivocal spots of measles on the neck and chest, which rapidly disappeared, the lungs became quickly involved.[3]

Rilliet[4] reports a case of severe measles without eruption in a child, aged twenty-one months, who contracted the disease twelve days after other cases in the same family. There were fever, coughing and sneezing, but the eruption did not appear. On the fourth day a lobular pneumonia developed, the child succumbing on the eighth day. Some authors accept the statement that desquamation may occur in measles without eruption. We contend, as in the case of scarlet fever, that

[1] Quoted by von Jürgensen: Loc. cit.
[2] Quoted in editor's notes in Bulkley's American edition of Gregory's Lectures, 1851.
[3] London Med. Gaz., June, 1850, p. 572. Cited by Bulkley: Loc. cit.
[4] Barthez and Rilliet, p. 249. Cited by von Jürgensen.

desquamation does not occur without some antecedent structural change in the skin, and that when desquamation occurs it signifies that a rash has existed which was unobserved.

There are *mild* cases of measles in which all of the usual phenomena are present, but in an extremely moderate, and sometimes imperfect, degree. The maximum temperature in such cases does not exceed 102° F. and the fever lasts but four or five days. The eruption is faint, poorly marked, of short duration and often so indefinite as to require other evidence to establish the diagnosis. The catarrhal symptoms are also slight, but present more uniformity than the cutaneous manifestations. This form is apt to be unattended by complications and the prognosis is extremely favorable.

Severe and Malignant Measles.—Measles of unusual severity may occur in isolated instances in ordinary epidemics, or the disease may prevail at times in severe form. The factors which determine malignancy are in some instances weakness, debility and bad hygienic surroundings of the patient, and probably in others an intense virulence of the infection. There are severe cases which are characterized by a normal course of the disease, but exhibit an unusual intensity of all of the symptoms. The fever, catarrhal symptoms and eruption may all be excessively developed. In the severe and fatal epidemic which we observed some years ago there was a general tendency to intense confluence of the eruption, so that on the second or third day the rash became quite scarlatinal in appearance.

In some cases characterized by great initial severity the system seems to be overwhelmed by the poison of the disease. The temperature soars to great height (105° to 107° F.), there is profound prostration, great restlessness alternating with stupor and the patient succumbs before the appearance of the rash. In these *toxemic* cases the diagnosis may be extremely difficult, and, unless elucidated by the history, quite impossible.

Severity may also be manifested by the early development of *pulmonary complications*. The first few days of the invasive stage may be quite normal, but suddenly the lungs become attacked and a fatal result rapidly ensues.

In the so-called *typhoid* form of measles the disease is ushered in with high fever and great prostration. The skin is hot and dry; there is great thirst and marked muscular relaxation. Nervous symptoms are pronounced, the patient being either apathetic and somnolent or delirious. The tongue is dry and furred, the lips glazed and the teeth covered with sordes. The abdomen is tender and distended and the bowels often loose. The eruption is poorly developed and bluish in appearance. These cases are usually fatal, death taking place within a week or, less commonly, convalescence may occur after a tedious and protracted illness.

Such cases as the above were not rare during the Civil War. *Camp measles* does not differ essentially from measles seen among civilians

save that as a result of privation and exposure the disease is apt to assume a more severe form. Measles is one of the most formidable of camp diseases, as is attested by the morbidity and mortality statistics of the Civil War of 1861. Bartholow says: "In one regiment which came under my observation every man contracted measles who had not had it in early life." The disease was much more prevalent in

FIG. 110.—Severe measles.

regiments recruited from country districts. This was also observed in the World War. The mortality-rate was high. In the general field hospital at Chattanooga it was 22.4 per cent, and in the General Hospital No. 1 at Nashville it was 19.6 per cent.

MALIGNANT HEMORRHAGIC MEASLES.—Black measles was, according to the descriptions of the older writers, much more common years ago than at the present day. It is also much rarer than hemorrhagic

smallpox, with which it has certain features in common. Hemorrhagic measles is more apt to develop in previously ill and debilitated subjects.

The onset of the disease is usually violent, the fever being high and nervous symptoms prominent. The eruption is bluish or purplish in color and fails to disappear upon pressure. In other cases the exanthem may appear, recede rapidly and be followed by hemorrhagic extravasation into the skin in the form of petechiæ or ecchymoses. At the same time bloody discharges occur from various mucous membranes. There is commonly severe epistaxis and blood may be observed in the urine, stools and vomited matter. The patient becomes rapidly exhausted, the pulse is frequent and thready, the skin pale and cold and death closes the scene.

It must not be supposed that all hemorrhagic eruptions in measles are necessarily in malignant cases. Attention has already been called to hemic extravasation into the skin in attacks of average severity.

Irregularity in the Origin and Spread of the Measles Exanthem.—The spread of the eruption of measles involving in succession the face, chest, neck, abdomen, arms, legs, etc., is a tolerably uniform and diagnostic phenomenon. Occasionally a departure from this normal progression takes place. The eruption may, in rare cases, be limited to the face or to the face and trunk. It may begin on the trunk or extremities and involve the face and neck only later. Mayr[1] states that the application of irritants to the skin, such as the use of lotions, ointments, bandages and compression from other causes may determine the point of origin of the eruption. He is also authority for the statement that in paraplegia from vertebral disease the rash is often absent on the paralyzed lower extremities.

Chairou[2] reports a curious abnormality of the measles eruption which occurred in a severe epidemic of measles at Rueil in 1862. The eruption lacked intensity, but was accompanied by profuse perspiration and a vesicular eruption similar to the miliary rash seen in lying-in women. Chairou proposed for this condition the name of sweating measles. The constitutional symptoms were severe and uncommon. The course was that of a septic or typhoid measles, with many complications observed in typhoid fever, such as periosteal trouble leading to necrosis of the maxillary bones, etc. The mortality-rate was high.

Recession of the Rash.—It occasionally happens that the measles exanthem suddenly and prematurely fades after reaching its maximum or even before the height of the eruption is attained. The recession of the rash may be temporary, the eruption later reappearing, or it may be permanent. The lay community has a traditional dread of this "striking in" of the eruption, fearing the involvement of one of the internal organs. As a matter of fact the sudden fading of the exanthem is not the cause, but the result of such condition. The phenomenon

[1] Loc. cit., p. 163.

[2] Essay awarded a prize by Academy of Medicine of Paris, cited by Trousseau (Loc. cit., p. 185).

is usually due to severe pulmonary involvement, leading to cardiac failure and consequent crippling of the circulatory apparatus. The skin becomes pale and the eruption fades either completely or shows itself as indistinct, bluish spots. With an improvement in the heart action the spots naturally acquire more color and the eruption, so to speak, returns. Thomas believes that rapid disappearance of the eruption does not necessarily indicate the development of some complication. He says: "I have never had an opportunity to convince myself of the connection of a speedy fading of the spots with the sudden occurrence of a complication. A simple rapidly progressing paleness of these can certainly not be considered anomalous."

Postrubeolic Eruptions.—Reference has already been made to the occurrence of a morbilliform rash, associated at times with renewed fever, developing after convalescence from measles. In rare cases other eruptions may make their appearance about this time. Roger[1] has seen cases, both of recurrent measles and also accidental erythematous rashes after measles. He reports an instance of the latter in a young woman twelve days after an attack of measles and another in an infant, aged two and half months, thirty-eight days afterward.

Meyer-Hoffmeister[2] saw a scarlatiniform erythema during convalescence from measles.

COMPLICATIONS AND SEQUELÆ OF MEASLES.

Larynx.—Catarrhal Laryngitis.—A moderate grade of catarrhal laryngitis is uniformly present in measles, and is, therefore, scarcely to be regarded as a complication. The laryngeal symptoms develop early in the invasive stage, giving rise to hoarseness, frequent cough and occasionally spasmodic dyspnea. The cough is dry, loud and hollow in tone, and in the beginning unproductive of expectoration. The paroxysms of coughing are often violent and incessant, seriously interfering with sleep. Upon the appearance of the cutaneous eruption the cough becomes looser and less frequent and is accompanied by expectoration. Holt states that severe catarrhal laryngitis is present in about 10 per cent of all cases of measles.

Ulcerative Laryngitis.—Ulcerative laryngitis occurs in a certain proportion of severe cases. In such instances the inflammation is so intense as to lead to necrosis of the mucous and submucous tissues. The vocal cords are commonly involved in the destructive process. Barthez and Rilliet found ulcerations and erosions in almost one-half of the cases of measles that came to autopsy. Pseudo-membranous deposits were present in about one-fifth of the cases.

Gerhardt[3] has seen these ulcerations by laryngoscopic examination during life. He has found them particularly upon the posterior wall

[1] Loc. cit., p. 875.
[2] Quoted by Thomas: Loc. cit., p. 90.
[3] Lehrb. d. Kinderh., p. 63.

of the larynx in cases that exhibit marked stenosis. They may be seen at times early, but are more commonly observed during the eruptive stage. The superficial ulcerations give rise to a rough, dry, frequently repeated cough, accompanied by spasmodic attacks. There is pain upon coughing, speaking or swallowing and often considerable dyspnea.

The most dangerous form of laryngitis is that accompanied by the formation of a pseudo-membrane, the so-called *membranous laryngitis*. The fatality of this complication is frightful. In the Hôspice des Enfants Assistés in Paris, Granlou[1] found this complication 235 times among 1633 cases of measles; out of these 235 patients 218 died, a most appalling mortality.

We have seen a number of these cases that had to be intubated; they all succumbed to the disease. Holt has collected 35 cases of membranous laryngitis out of 2837 cases of measles from miscellaneous sources; he remarks that this complication is more frequent than this in institution epidemics.

Membranous laryngitis may result from the action of the streptococcus, the diphtheria bacillus and perhaps other organisms. Holt states that when the membrane forms in the larynx at the height of the disease it is almost always of streptococcic origin; when it develops at a later period it is usually due to the Klebs-Loeffler organism. The majority of cases appear to be due to pyogenic bacteria. The false membrane is not always limited to the larynx, but may invade the fauces, nose and mouth. The laryngeal stenosis usually comes on gradually, although more commonly the symptoms may be sudden in their appearance.

The dyspnea frequently becomes so alarming as to necessitate intubation or tracheotomy. These procedures, however, give, as a rule, but temporary relief, for a fatal bronchopneumonia is almost sure to develop.

The diagnosis between true *laryngeal diphtheria* and membranous laryngitis of streptococcus origin can only be indubitably settled by a bacteriological examination; the former condition is apt to develop late and the latter at the height of the disease. The prognosis appears to be equally desperate in both conditions.

Lungs.—The trachea and larger bronchial tubes are so commonly involved in the catarrhal process in measles that a moderate grade of *tracheitis* and *bronchitis* may be regarded as belonging to the normal symptomatology of the disease. It is only when the inflammatory disturbance is intense and downard extension takes place that the complication assumes a serious aspect. Severe bronchial catarrh usually manifests itself just at or after the height of the eruptive stage; if it be sufficiently widespread the fever, which at this time falls, will continue to remain elevated. There is frequent coughing, accompanied by muco-purulent expectoration.

[1] La rougeôle à l'Hospice des enfants assistés, Paris, 1892.

Bronchopneumonia.—Bronchopneumonia is the most common and most fatal of all of the complications of measles. Other conditions fade into insignificance when compared to the slaughter that this complication occasions. Over a half century ago Gregory wrote: "I am sure I speak much within bounds when I say that nine-tenths of the deaths by measles occur in consequence of pneumonia."

Bartels met with 68 cases of bronchopneumonia among 573 cases of measles, or 11.9 per cent; Ziemssen and Krabler report 50 attacks of pneumonia among 311 cases of measles, or 16.1 per cent. The figures of Embden give a much small incidence—27 attacks in 461 cases, or 5.9 per cent. The frequency of this complication seems to vary considerably in different epidemics. It is much more common in foundling

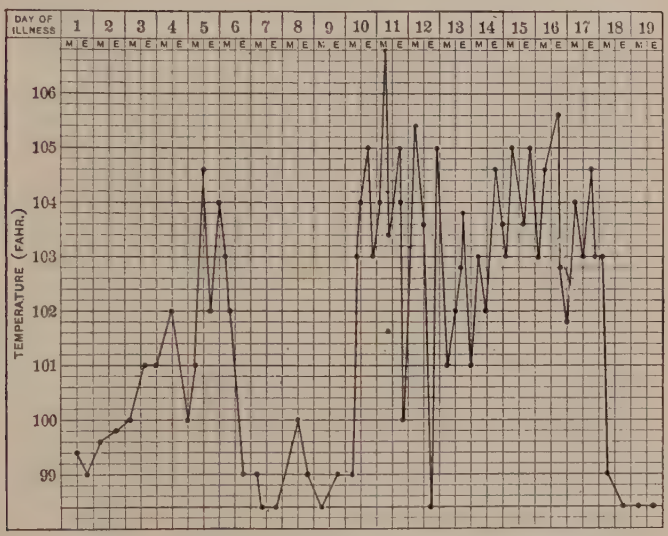

DAY OF ILLNESS
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19
M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E M E
TEMPERATURE (FAHR.)
106
105
104
103
102
101
100
99
Measles.
Pneumonia.

FIG. 111.—Boy, aged five years. (Tuley.)

asylums, orphanages and similar institutions. It is more apt to attack feeble and poorly nourished children and those debilitated by previous illness. This complication is particularly prone to attack children under two years of age. Holt states that in two epidemics in the Nursery and Child's Hospital, embracing about 300 cases, nearly all in children under three years of age, bronchopneumonia occurred in about 40 per cent of the cases. Of those who had pneumonia, 70 per cent died. Henoch says that a certain amount of pneumonia is seen in nearly all fatal cases of measles.

Bronchopneumonia usually manifests itself when the eruption begins to decline, although the onset may be delayed to a later period. The posteruptive decline in the temperature fails to occur, the fever instead

remaining in the neighborhood of 103° F., with, perhaps, morning remissions of 1° F. or so. The pulse is greatly increased in frequency, and the respiration is shallow and hurried, and not infrequently labored and difficult; it is a pitiful sight to see the little patient with dilating nostrils and a livid countenance raise itself in the bed to relieve its distressed breathing. The cough may be short and repeated or infrequent and spasmodic. In unfavorable cases there is protracted fever, progressive increase in the rapidity of respiration (60 to 80), cold extremities, extreme weakness and rapid-running pulse. Nourishment is refused, and when taken is often vomited. Great pallor develops and toward the end a characteristic lividity is seen. A few hours before death the temperature may rise to great height, 107° or 108° F. In favorable cases the temperature at the end of ten days or two weeks declines gradually to normal, the cough lessens, the respiration improves, the child becomes brighter, desires more food and takes an increasing interest in its surroundings.

The symptoms that indicate the presence of a bronchopneumonia are protracted fever, cough, rapid pulse, hurried and labored breathing and prostration. Percussion will often discover some dulness over one or both of the lower lobes posteriorly; the respiratory murmur is diminished and broncho-vesicular breathing is heard; in addition to the coarse rales heard in the larger tubes, fine, moist rales are audible over the small, consolidated areas.

Lobar Pneumonia.—Lobar or croupous pneumonia is a much less frequent complication of measles than the catarrhal form, and is apt, when it occurs, to develop in older patients. This form of pneumonia is characterized by higher fever with fewer remissions, by its limitation to one lung or lobe thereof, by the presence of pleuritic pains, a shorter course terminated by crisis and a lower mortality-rate.

Pleurisy.—Pleurisy with effusion is an unusual complication of measles. In some epidemics it may develop secondarily to a severe pneumonia, in which case it is apt to eventuate in an empyema.

Fürbringer[1] calls attention to the occasional occurrence of a primary pleurisy with effusion. He has observed a number of cases, most of which ran an acute course and were probably purulent from the beginning.

Pulmonary Tuberculosis.—Pulmonary tuberculosis may manifest itself as a termination of a long-standing bronchopneumonia occurring after measles. The bronchial catarrh and the lowered resistance of the patient render the implantation of tuberculosis readily explicable. In cases in which a latent glandular tuberculosis, particularly of the thoracic lymph nodes, has existed, the attack of measles stimulates the previous disease to noxious activity. In some cases tuberculosis may develop as a direct sequel of measles an irregular temperature persisting after the incomplete convalescence from the latter disease. The tuberculous disease may take the form of an acute miliary tuberculosis.

[1] Eulenberg's Real Encyclopedia, 2d ed., **12**, 559, quoted by von Jürgensen.

Holt truly says: "An attack of measles in a child with tuberculous antecedents should always be looked upon with apprehension."

Barthez and Rilliet have observed *gangrene of the lungs* in 4 instances, and Steiner and Neureutter have met with this complication in 2 patients. This much-to-be-dreaded condition may have its origin in a severe bronchopneumonia.

Alimentary Tract.—From what has already been said concerning the measles exanthem it is evident that a mild inflammation of the buccal and pharyngeal mucous membrane is uniformly observed. This comes on in the invasive stage and tends to subside as the cutaneous eruption increases in development.

The cheeks, gums, tongue, soft palate, tonsils and pharyngeal wall all participate in the catarrhal process. In feeble and debilitated children this inflammation, especially under the influence of infection with pyogenic and other bacteria, may lead to complications which are not only subjectively distressing, but of serious import. *Aphthous stomatitis* has been reported by a number of writers. The sores may give rise to much pain and interfere with the desire of the child to take nourishment. *Ulcerative stomatitis* not infrequently develops, particularly in the bucco-gingival furrow. This is characterized by the formation of small patches covered with grayish, necrotic epithelium. When the dead epithelial covering is cast off there are disclosed to view ulcerations of varying depth, with sharp and irregular edges; the base is frequently covered with a pseudo-membranous deposit. These losses of tissue are not infrequently seen on the gums and about the lips, particularly the oral commissures; in the latter regions each movement of the mouth causes pain and induces bleeding. In poorly nourished children these ulcerations may last for a long time before complete healing occurs.

A fortunately rare but most frightful complication of measles is that form of gangrene variously designated *cancrum oris, gangrenous stomatitis, or noma*. The fatal character of this complication makes the condition of sufficient importance to warrant a description elsewhere. To be sure, there are less serious forms of gangrenous stomatitis in which the loss of tissue is circumscribed. We have not infrequently seen necrosis of a portion of the gum and subjacent alveolar process which, after the throwing off of the slough, has been followed by thorough healing; in some of these cases a portion of the bone and the neighboring teeth have come away.

In a certain proportion of cases *membranous patches* may be seen on the tonsils and neighboring palatal mucous membrane. This process may spread downward into the larynx and give rise to the dreaded membranous laryngitis. The pseudo-membrane may be of streptococcic or staphylococcic origin like the exudate seen in scarlatina, or it may be true diphtheria. In some cases *tonsillitis* is observed, in which event there is enlargement and congestion of these structures and pain upon swallowing.

The stomach is but rarely the seat of any serious complication.

Diarrhea.—Diarrhea is a common and not infrequently a serious accompaniment of measles. It may exist in all grades, from a slight catarrhal enteritis, lasting but a few days, to a severe entero-colitis with fatal outcome. As would naturally be expected, diarrhea is more common in the summer months and especially in extremely hot summers. This complication is also more frequently observed in tropical and subtropical countries. Gregory says: "In India and other hot countries thoracic complications are rare; diarrhea and dysentery prove the usual and most troublesome sequelæ." It is not at all uncommon for a mild diarrhea to be present in the invasive and early eruptive stages. There are frequent loose and watery movements, with or without pain, which tend to subside as the eruptive stage advances. The severe forms of enteritis and ileo-colitis usually develop late during the decline of the eruption. In some cases the large intestine is involved and symptoms of dysentery manifest themselves; pain and tenesmus are present and frequent; small, bloody stools containing mucus are passed.

Diarrhea appears to be more common in some epidemics than in others. Willischanin[1] observed an epidemic of measles in a girls' school in which 10 out of 50 of the patients had diarrhea during convalescence. It lasted from three to five days and was believed to be due to the elimination of special toxins.

Intestinal inflammation is most frequently observed in infants and young children, in whom it not infrequently leads to a fatal termination. Cases are on record, however, in which adults have succumbed to measles as a result of this complication.

Spleen.—Observations concerning enlargement of the spleen during the eruptive stage of measles were made by Bleyer[2] in 396 cases. Of 47 patients who were examined the day before the rash appeared, the spleen was enlarged in 2 per cent; of 58 patients examined on the first day of the rash, 24 per cent had enlarged spleen; and of 80 examined on the second day, the spleen was palpable in 43 per cent. Enlarged spleens were found in 56 per cent of 62 patients examined on the third day and in 52 per cent of 49 patients examined on the fourth day of the eruption. This enlargement of the spleen was coincidental with the eruptive stage of this disease, both as to appearance and disappearance, the greatest enlargement both as to frequency and size being noted on the third and fourth days of the rash. The severity of an attack did not affect the incidence of enlargement.

Fort[3] has likewise directed attention to enlargement of the spleen in measles, and this sign is looked upon as having diagnostic value, even though it has curiously enough hitherto escaped attention in this respect.

Nervous System.—As is the case with most infectious diseases, measles may be accompanied or followed by a great variety of dis-

[1] St. Petersburger med. Wchnschr., December 4, 1893. Quoted by Williams: Loc. cit.
[2] Am. Jour. Dis. Child., 1926, **31**, 26. [3] Jour. Am. Med. Assn., 1926, **86**, 1567.

turbances due to involvement of the brain, spinal cord or the peripheral nerves. When the fact is recognized that measles attacks almost the entire human family, the relative infrequency of nervous complications may be appreciated.

Mental Disorder.—Measles is, in rare instances, followed by insanity, which usually takes either the form of mania or dementia. Christian[1] reports a case of temporary mania and paralysis. Finkelstein[2] saw 2 cases of mania after measles, and Bond[3] observed a case developing on the eight day of the disease. Weber noted delusions of persecution in one of his patients. In an epidemic of 108 cases occurring in an institution in Virginia and reported by Smith and Dabney, insanity ending in recovery developed in 3 patients.

Beach[4] analyzed 2000 cases of idiocy and found 37 (1.85 per cent) which could be traced to attacks of infectious diseases; of this number, 11 were attributed to attacks of measles. Nearly all the cases, however, were in persons with neurotic antecedents.

Cerebral and Spinal Paralysis.—Paralysis following measles is a rare complication. Allyn[5] was able to collect but 41 instances, 35 of which were palsies of cerebral origin. The onset of the complication is abrupt, and commonly, though not always, marked by convulsions. In other cases somnolence or coma occurs in the beginning. Following upon the convulsions or coma the evidences of paralysis are observed. In spinal paralysis coma and convulsions are absent. The paralyses, according to Allyn, usually appear during convalescence and most frequently from the latter part of the first to the close of the third week after the onset of the attack. Of 21 reported cases, 11 developed palsy between the fifth and sixteenth day, while 5 more probably belong to this period, although the data are imperfect. In the remaining cases 3 developed convulsions on the second day of the eruption, 1 a month after the onset of the measles and 1 in from five to six weeks. The prognosis as to life is good. In only 4 of the cases did a fatal result ensue. In some of the cases the lesions were more or less permanent, aphasia and muscular atrophy persisting some years after the attack. The paralyses collated by Allyn were chiefly cerebral palsies of the hemiplegic type, but included also disseminated myelitis and ascending spinal palsy.

Cases of paralysis have since been reported by a number of authors. Dawson Williams[6] saw a case of disseminated sclerosis in a girl three years of age on the fourth day of an attack of measles.

Bruce records a case of diffuse myelitis and Barlow an extensive softening of the cord. Ormerod observed paralytic symptoms one month after measles in 3 children. Andeoud and Jaccard[7] report a

[1] Centralbl., 1874, p. 95.
[2] Vrach, 1898, No. 20.
[3] Maryland Med. Jour., January 29, 1898.
[4] Brit. Med. Jour., 1895, ii, 707.
[5] Med. News, November 28, 1891.
[6] Med.-Chir. Soc., November 28, 1893.
[7] Rev. méd. de la Suisse, 1894.

a case of vesical paralysis in a girl nine years of age, and Ortholob[1] a true paraplegia in a girl three years of age.

Paralysis after measles has also been reported by Graf,[2] Morton[3] and Ellison,[4] who observed a case of acute ascending myelitis.

False Disseminated Sclerosis.—There occasionally occurs in measles, as in smallpox and other infectious diseases, sudden unconsciousness followed by loss of power of speech and certain other paretic and ataxic symptoms. This may occur during the febrile stage or during convalescence. Rapid recovery may ensue or a train of symptoms may develop suggesting disseminated sclerosis. Instead of the condition being progressive there is a distinct tendency to improve.

Barthez and Sanné have collected a series of 8 cases characterized by paresis of the soft palate, pharynx, tongue and muscles of the neck. In 4 cases the symptoms appeared early in the course of measles and in the remaining 4 at the end of three weeks. Recovery took place in all of the cases in from three to twenty days.

Meningitis.—Instances of inflammation of the membranes of the brain have been reported by Spiess, Voit, Meyer-Hoffmeister, Kellner, Constant, Löschner, Thore, Bufalini, King, Mettenheimer and Harvey.[5] Frank, Rilliet and Starck have observed spinal meningitis after measles.

Chorea.—Chorea is an occasional sequel of measles. Cases have been recorded by Sibergundi, Böning and others. In an analysis of 439 cases of chorea made by Stephen MacKenzie for the Collective Investigation Committee of the British Medical Association, measles or measles and anemia were found to be the sole antecedent illnesses in 49 cases—nearly 9 per cent. Barthez and Rilliet have noted after measles a prompt recovery from a chorea of some months' duration.

Skin.—Mention has already been made of the accidental erythematous rashes which may, in rare cases, precede or follow the true exanthem of measles.

During the invasive period it is not rare for *herpes facialis* to appear, a phenomenon which develops in many infectious processes. *Urticaria* may also occur either in the course of the disease or at a later period. The urticarial eruption is usually moderate and of short duration. Claus[6] reports urticaria occurring in two cases of measles during the period of incubation.

Several authors have called attention to the development of a *bullous eruption* resembling pemphigus. Cases have been reported by Krieg,[7] Löschner, Henoch,[8] Steiner,[9] Du Castel[10] and by Baginsky.[11] Steiner

[1] Thèse de Bordeaux, November 23,1894.
[2] Indiana Med. Jour., 1892 and 1893, p. 176.
[3] Arch. Pediat., 1897, **14**, 541.
[4] Lancet, 1896, ii, 1077.
[5] Jour. Am. Med. Assn., 1897, **29**, 1149. The other authors mentioned are quoted by Thomas.
[6] Jahrb. f. Kinderh., June, 1894.
[7] Cst. Jahrb., 1843, p. 219.
[8] Berl. klin. Wchnschr., 1882, p. 193.
[9] Jahrb. f. Kinderh., vol. **7**, 346.
[10] Rev. gén. de clin. et de thérap., 1897, **7**, 346.
[11] Arch. f. Kinderh., 1900, vol. **28**.

saw 4 cases, all in the same family. The blebs varied in size from a pea to a pigeon's egg, came out in crops, attacked both the skin and mucous membranes, were accompanied by fever and occurred at any time during the course of the disease, before, during or after the measles exanthem.

In Henoch's[1] patient the bullæ were so large that a single one covered each cheek; 2 out of these 5 cases terminated fatally. Masarei[2] saw upon the palms and soles during desquamation large blebs which burst and left obstinate and painful ulcers.

Gangrene may attack other parts of the skin than the cheek and genitalia, which are the most common sites of the process. Thomas, of Paris, has reported an extensive gangrene of the buttocks in a child two years of age. Mayr, Faye, Battersey and Carroll[3] report instances of gangrene attacking various portions of the cutaneous surface.

Impetigo, boils and abscesses are occasionally observed during convalescence from measles. They represent varying grades of infection with the common pyogenic organisms. *Eczema* occasionally makes its initial appearance after an attack of measles and may persist for an indefinite period. On the other hand, chronic eczemas have been known to disappear after an attack, as in cases reported by Behrend and others. *Psoriasis* has been observed to appear for the first time after measles. Measles, of course, does not cause the psoriasis, but merely determines the date of its outbreak.

Disseminated tuberculosis of the skin may follow in the wake of measles, as in the cases reported by Du Castel,[4] Haushalter[5] and Adamson.[6]

Du Castel saw 3 cases and remarks that "It is not exceptional to see a disseminated tuberculosis of the skin as a sequel to measles." This usually attacks the face, legs and especially the upper extremities. The lesions appear soon after the decline of the measles eruption in the form of small, deep-red nodules. Haushalter saw 2 cases of scrofulous lichen, 1 of which later developed enlarged glands and tuberculous gummas. Adamson's case was one of multiple warty lupus occurring on the arms and legs. The patient subsequently developed a post-pharyngeal abscess and later hip disease.

Roger[7] observed, in the spring of 1900, 4 cases of *erythema nodosum* after attacks of measles. A girl, aged seventeen years, eleven days after the termination of an attack of measles of moderate intensity, developed fever and twenty-four hours later a typical erythema nodosum of the legs and subsequently the arms, accompanied by painful joints; the condition lasted fifteen days.

The other 3 cases were analogous; they occurred in patients fifteen, seventeen, and twenty-six years of age, respectively. Fever appeared

[1] Mentioned by von Jürgensen: Loc. cit., p. 300.
[2] Quoted by Thomas.
[3] Ibid.
[4] Ann. de dermat., 1898, **9**, 729.
[5] Ibid., No. 5, p. 455.
[6] Brit. Jour. Dermat., 1899, p. 20.
[7] Loc. cit., p. 875.

from nine to ten days after the termination of measles. The erythematous nodes and the joint involvement persisted from seven to ten days.

Eyes.—Ocular complications are not rare in measles, a fact which is easily explained by the severe catarrhal involvement of the conjunctiva during the invasive and eruptive stages. The eyes are particularly apt to suffer in scrofulous children. Corneal ulcerations may occur and in bad cases lead to perforation and general panophthalmitis. It is not rare for obstinate blepharitis, granular lids, or keratitis to persist a long time after convalescence from the original disease. Comby states that proper care of the eyes greatly reduces the number of ocular complications, and in support thereof mentions the fact that he observed only 17 cases of conjunctivitis of moderate intensity among 715 cases of measles.

Ears.—Inflammation of the middle ear is by no means an uncommon complication of measles, although it does not develop as frequently as in scarlatina. The catarrhal inflammation of the nasal passages frequently extends along the Eustachian tubes to the middle ear. Bezold[1] carefully explored the ears in 16 fatal cases of measles, in all of which he found inflammatory changes. The tympanic cavity contained either a muco-purulent exudation or a material that was frankly puriform. The streptococcus pyogenes was present in about 50 per cent of the cases; in the other half the Staphylococcus aureus and albus were found. The mucous membrane is red, swollen and covered with a muco-purulent or sero-purulent exudate. Tobietz[2] examined the ears of 22 cases of measles at autopsy and confirmed the above-mentioned findings.

Both of these writers are in accord as to the early development of the aural catarrh. The ear trouble is not regarded as due to a secondary infection, but is rather the result of the localization in this region of the enanthem. Catarrhal otitis may, therefore, develop in the early eruptive period. In a case studied by Tobietz that died twenty-four hours after the appearance of the eruption otitis was already present.

This early otitis is comparatively mild and usually does not lead to perforation of the tympanic membrane. The later-developing otitis media usually results from infection from the naso-pharynx, and is much more prone to end in suppuration and perforation.

Severe purulent otitis media appears to be more common in some epidemics of measles than in others. Downie[3] states that children who have adenoid vegetations and suffer from catarrh of the throat and nose are more apt to develop middle-ear trouble. He furthermore claims that the horizontal posture of the sick child favors Eustachian infection and retention of the inflammatory products within the middle ear. Of 501 cases of tympanic involvement in children seen by Downie, the condition was attributable to measles in 131 instances, or 26.1 per cent. Curiously, only 63 cases (12.6 per cent) were observed that developed during an attack of scarlet fever.

[1] München. med. Wchnschr., March, 1896.
[2] Quoted by Comby: Loc. cit.
[3] Brit. Med. Jour., 1894, ii, 1163.

It is not always easy to diagnose the onset of an otitis media, particularly in young children who are unable to make verbal complaint. The complication most commonly develops about the end of the second week. Children are cross and fretful, frequently toss the head and cry out with pain. The temperature is usually elevated and may rise to great height. When an otherwise inexplicable rise of temperature occurs about this time the possibility of purulent otitis must be considered. Inspection of the tympanic membrane is not an easy task in young children. When this can be accomplished the membrane is seen to be congested and lusterless, and when pus is present the tympanum bulges into the meatus, the puriform secretion shining through the lower tympanic segment.

In severe cases of middle-ear disease necrosis of the ossicles or of the surrounding bony walls may take place. Burkner[1] says: "An invasion of the labyrinth by cocci causing necrosis has been repeatedly demonstrated of late. The lesion results in a very serious loss of functional power." The suppurative inflammation may extend to the mastoid cells or, in rare cases, to the membranes of the brain. Ashby and Wright have pointed out the fact that infection may take place through the petromastoid suture, which in infancy is still ununited. Purulent meningitis, abscess of the brain or thrombosis of the lateral sinus might thus develop. In general, it may be stated that middle-ear trouble complicating measles is less serious than that which occurs in scarlet fever.

Many cases of *deaf-mutism* are traceable to attacks of measles. Kerr, Love and Addison[2] have collected statistics from institutions in Great Britain which show that of 1140 deaf-mutes, 138, or 9.8 per cent, attributed their loss of hearing to attacks of measles. Of 1673 acquired cases in American institutions, 52, or 3.1 per cent, were due to measles. Among 1989 acquired cases on the continent of Europe, 84 cases, or 4.2 per cent, were ascribed to this disease.

In these cases the deafness results from destructive changes in the internal ear which have resulted from extension of the inflammatory process from the middle ear.

The Heart.—Endocarditis, pericarditis, and myocarditis are rare complications of measles. Inflammation and degeneration of the cardiac muscle may occur in malignant cases, particularly when there is hyperpyrexia. We recall a malignant family epidemic some years ago which destroyed the lives of the 3 children of the household. One child sat up in bed during convalescence and dropped back dead. The other 2 succumbed to a profound toxemia.

Cases of *endocarditis* have been reported by Martineau, West and Köbler. Hutchinson[3] records 4 cases in which mitral murmurs devel-

[1] Behandlung der bei Infectionskrankheiten Vorkommenden Ohraffectionen, Loc. cit., p. 581.

[2] Deaf-mutism, a Clinical and Pathological Study, Glasgow, 1896. Cited by Dawson Williams: Loc. cit.

[3] Med.-Chir. Trans., 1891, vol. 24.

oped during the course of measles, and Cheadle refers to 2 cases found in the postmortem records of Great Ormond Street Hospital. Comby discovered mitral insufficiency in a girl, aged nine years, after an attack of measles. Although Sansom[1] states that the influence of measles in predisposing to endocarditis has been much underrated, most writers are of the opinion that this complication is a rarity.

Pericarditis, according to Autenrieth, is not infrequent. Cases have been reported by Berndt, Majer, Espinouse, Braun, Siegel, Mettenheimer and Heyfelder.[2] When pericarditis occurs it is apt to be associated with a pleuropneumonia.

Kidneys.—Renal complications are rare in measles, their infrequency contrasting sharply with their prominence in scarlatina. Nevertheless, Baginsky says that his experience leads him to believe that they would be discovered more often if carefully looked for.

Febrile albuminuria of brief duration is not uncommon in well-pronounced attacks of measles, as it is in other infectious processes accompanied by fever. When the kidneys are seriously involved there may be general anasarca, as in cases reported by Abeille, Denizet and Comby (2 cases). Ascites and anasarca may, however, occur without albuminuria, at times in association with chronic diarrhea.

Cases of true nephritis have been placed on record by Geissler, Röser, Frank, Rilliet, West, Kjellberg, Lehman, Bouchut, Malmsten, Spiess, Hauner, Steiner, Neuretter, Zehnder and Thomas, who cites these various writers. Fatal cases with uremic symptoms have been reported by Müller, Demme, Browning and Zichy-Woinarski.[3]

Vulvitis.—Among 715 cases of measles treated in isolation pavilions, Comby observed vulvitis 25 times, an incidence which he thinks was kept relatively infrequent through systematic antiseptic irrigations. The inflammation of the vaginal orifice and vulva begins early, as a rule, and may persist for some time. The parts are red, swollen, covered with a muco-purulent discharge and extremely tender. Micturition is accomplished with considerable pain. In some cases vulvar ulceration occurs and more rarely gangrene

Glands.—A moderate grade of adenopathy is a part of the normal symptomatology of measles. In some cases the lymphatic glands become greatly enlarged, particularly in the cervical region. In rare cases suppuration may take place, as in cases mentioned by Gregory and Rilliet.

In other cases the glandular enlargement may persist for a long time and eventually terminate in glandular tuberculosis. This is particularly true of the bronchial glands. Fichtbauer, Thore, Eiseman, Bufalini and Battersey[4] have reported cases of inflammation of the parotid gland accompanying measles, and Seidl, Schultze and Kellner have seen the parotids involved at a later period.

[1] Quoted by Williams: Loc. cit.
[2] Mentioned by Thomas: Loc. cit.
[3] Australian Med. Gaz., October 15, 1893.
[4] Quoted by Thomas.

Purpura.—Hemorrhages developing late in the course of the disease or during convalescence should not be interpreted as evidence of malignant hemorrhagic measles, but as a secondary and superadded condition. Nearly all of the exanthemata may at times be complicated at a late stage by the development of hemorrhages into the skin and from the various mucous membranes, including the kidneys and intestines.

Masarei[1] saw 8 patients convalescing from measles attacked with fever, dropsy without albuminuria and "scurvy, mostly in the form of purpura;" of of the cases ended fatally. Gley[2] saw intense purpura hæmorrhagica, together with scorbutic appearances in the mouth, some days after the disappearance of the measles rash.

FIG. 112.—Fatal cancrum oris after measles. The necrotic tissue has been removed, exposing to view the alveolus and teeth.

Gangrene.—Although gangrene is not a common complication of measles, it appears to occur more often after this infection than any other, excepting, of course, cutaneous gangrene in smallpox.

The necrosis is apt to take the form variously designated as *cancrum oris, gangrenous stomatitis, or noma*. This formidable complication commonly develops during the decline of the eruption. It is often associated with or preceded by an ulcerative stomatitis. The symptoms that first attract attention are salivation and a fetid breath. If the mouth is inspected there will usually be found, between the commissure of the mouth on the affected side and the opening of Steno's duct, a vesicular elevation of a violaceous color; this becomes gradu-

[1] Quoted by Thomas, p. 104.

[2] Quoted by Thomas.

ally darker and finally gives way to a blackish, pultaceous mass. The corresponsing portion of the cheek on the exterior is swollen and of a wax-like pallor. Soon a bluish-red spot appears, which becomes gangrenous and breaks through. From this point the necrosis now spreads in all directions. The spreading border is surrounded by a dusky-red zone which is firm and infiltrated. The immediate spreading edge

FIG. 113.—Cancrum oris after measles.

FIG. 114.—Cancrum oris complicating measles. Photograph taken two days after the cutaneous tissues became involved.

shows a raising up of the epidermis in the form of a vesicular ring. There may be an extension of gangrene from $\frac{1}{4}$ to 1 inch in twenty-four hours. The gangrenous process in severe cases involves the entire cheek and the greater part of the nose and lips. It has been known to attack the ear, the eyelids and a considerable portion of the neck. Usually the patient dies of exhaustion before such ravages are possible.

In a small proportion of cases the gangrene ceases, a line of demarcation is formed and the sphacelated tissues are gradually thrown off. In such instances the deformity must subsequently be remedied by a

FIG. 115.—Same patient as Fig. 114, showing the spread of the gangrene. Photograph taken three days after the previous picture.

FIG. 116.—Same patient as Figs. 114 and 115. Photograph taken after death on the eighth day after the beginning of the gangrene, and three days after Fig. 115.

plastic operation. In the fatal cases there is great prostration, the child takes nourishment with difficulty, and death takes place ordinarily in from one to two weeks. A horrible odor emanates from the patient, which pervades the entire room in which he lies.

There is a less serious form of gangrenous stomatitis in which the necrotic process is limited to the mucous membrane and bony tissues of the mouth. This commonly has its origin about the gums and alveolar process. After the loss of some of the teeth and a portion of necrosed alveolus, the process may cease and recovery take place. In some cases, however, this bony necrosis is merely part of the general gangrenous process which attacks the cheeks.

The necrotic process may, in rare cases, attack the genitalia, particularly of female children, giving rise to the condition known as *noma pudendi*. The course of the gangrene does not differ from that involving the mouth.

Measles has preceded about one-half of the cases of *cancrum oris* on record. In 106 cases of gangrene of the mouth Tourde found 41 to follow or accompany attacks of measles. Caillout and Bouley, in 46 cases of gangrene of the mouth, noted measles as an antecedent disease in 40 instances. Mahieux saw measles produce gangrene of the mouth in 3 out of 11 cases. Thus, in 163 cases of gangrene of the mouth measles preceded in 84, or over 50 per cent.[1]

Rilliet and Barthez observed 11 children with measles attacked with gangrene; the localization was as follows: Gangrene of the mouth, 8 times; gangrene of the lungs, 4 times; gangrene of the pharynx, 3 times; gangrene of the larynx, once. The gangrene appeared in several localities in some of the patients. Moynier saw 6 cases of gangrene in measles. In 4 cases the vulva was attacked, 2 dying. Gangrene was noted 5 times attacking the skin, the following regions being selected: Abdomen, face (twice), arm and buttock. A number of other cases of gangrene of the mouth were observed. Pneumonia and diarrhea were frequent complicating conditions.

Hildebrandt[2] and Perthes[3] from the literature have collected 133 cases of cancrum oris in which the antecedent or accompanying disease is mentioned. Noma accompanied or followed measles in 53 cases. The diseases are as follows:[4] Measles, 53 times; typhoid fever, 26 times; chronic diarrhea, 21 times; scrofula, 19 times; smallpox, 9 times; diphtheria and measles, twice; diphtheria and typhoid, once; diphtheria of the genitalia, once; diphtheria and scarlet fever, once.

The affection is extremely rare in infancy and beyond the age of puberty; it may be remarked that measles is also uncommon during these periods. Von Bruns[5] collected 413 cases of noma, among which only 6 cases occurred in infancy.

[1] Mentioned by Moynier, Des accidents graves de la rougeole, etc., Metz, 1860.
[2] Dissertation, Berlin, 1873. [3] Verhandl. deutsch. Gesellsch. f. Chir., 28 Kongress.
[4] Mentioned by Walsh: Diphtheria Bacilli in Noma, Proc. Philadelphia Path. Soc., June, 1901.
[5] Handbuch der praktikal Chirurgie, vol. 1, Sect. 2.

The cause of noma is but poorly understood. It has been variously attributed to embolism, nerve involvement, the use of mercury and infection with some necrotizing microörganism. The last-named theory is doubtless correct, although the identity of this microbe does not appear to have been determined.

Walsh[1] made a careful bacteriological study of 8 cases of noma occurring in a home for children in Philadelphia. It is an interesting fact that these cases occurred during a period of two and a half years. The diphtheria bacillus was recovered by culture from each case. Inoculation and tinctorial tests were employed to identify the Klebs-Loeffler organism. Most of the cases followed measles, but several occurred after diphtheria. Four of the cases began with ulcerative stomatitis. A number of the cases of ulcerative stomatitis—15 in all—were cultured, but diphtheria organisms were not found. Walsh states that "Since noma is a species of moist gangrene, requiring probably from analogy two different microörganisms, one a saprophyte to produce putrefaction, another a parasite to produce primary necrosis, it is possible that in these cases where diphtheria bacilli are found they may be the primary causative agents. When other pathogenic microorganisms capable of producing necroses are found it is possible that they may be the primary excitants."

The above investigation is of considerable interest, particularly in view of the painstaking manner in which it was carried out. The result, however, is scarcely in harmony with our clinical experience. We have observed 4 cases of fatal cancrum oris; 3 occurred with measles following scarlet fever, the other with measles alone. We have never had a case of noma develop in the diphtheria wards, although on a number of occasions measles has broken out there.

Noma is regarded by Matzenauer[2] as a form of hospital gangrene, but feebly contagious and requiring, as a rule, a severe preceding disease to produce a predisposition. He discredits the diphtheria bacillus as an etiological factor, and believes the exciting organism is the same anaërobic rod-shaped bacillus that is found in hospital gangrene.

One fact is undoubted, that measles for some reason more strongly predisposes to the development of noma than any other affection. Babes and Zambilovici[3] announce that they have discovered a very small bacillus, cultures of which injected into the cheek of a rabbit have given rise to gangrene similar to noma.

The mortality of noma is frightful, about 70 per cent of the patients succumbing to the disease.

Pregnancy.—Measles in *pregnant women* is uncommon, inasmuch as most individuals pass through an attack of measles in childhood. As is true of nearly all infectious diseases, the development of measles in parturient women is apt to prematurely terminate the pregnancy.

[1] Loc. cit.
[2] Arch. f. Dermat. u. Syph., 1902, No. 60, p. 373.
[3] Quoted by Roger: Loc. cit., p. 402.

Rösch has reported a case of abortion terminating fatally as a result of measles.

Incidental Improvement in Chronic Diseases After Measles.—Every infectious disease produces a certain systemic commotion or change; this may favor the development of diseases to which the patient may be inclined. On the other hand, existing diseases, sometimes of long duration, may disappear after such a systemic shaking-up. Thomas has collected a number of interesting instances from which we freely quote.

Behrend saw an eczema of the scalp of three-years' duration in a woman, aged forty years, permanently cured after an attack of measles. The curative influence of measles upon long-standing diseases of the skin has also been attested by Rilliet, Taupin, Guersent and Rayer. Barthez and Rillet saw chorea, epilepsy and incontinence of urine of several months' duration get well after measles.

Fig. 117.—Boy exhibiting eruption of measles which developed during convalescence from smallpox.

According to Weisse, a girl who suffered from convulsions was entirely cured. Guersent noticed, with the beginning of the fever of measles, permanent relief from epileptiform seizures, of which the patient had had several a day for a long time. Schmidt saw a girl, aged six years, who had had daily convulsions that had so reduced her strength that death was expected, completely recover after measles. Feith and Schröder van der Kolk report the case of a woman who for five years was confined to an asylum because of violent attacks of mania, who, after measles, was cured and discharged from the institution. Hildebrandt saw an obstinate disease of the joints, which had been unsuccessfully treated for three years, promptly get well after convalescence from measles. Schmidt noted an almost magical recovery in a boy, aged five years, with contraction of the lower extremities of six months' duration. Of course, such examples of the accidental curative influence of an attack of an infectious disease are met with

not only after measles, but also at times after other febrile processes. Mention is made elsewhere of a raving maniac, confined in an insane asylum, who was completely cured after an attack of smallpox.

Coincidence of Measles With Other Infections.—Measles may be complicated by almost any of the known infectious diseases. In the association of several infectious processes measles may be the primary disease, or it may develop secondarily after some other infection. We have, on a number of occasions, seen measles complicate diphtheria and scarlet fever. We are inclined to believe that the prognosis is more serious when measles is the secondary infection than when some other disease is engrafted upon it. We have seen measles develop during convalescence from smallpox and have also observed the reverse order.

In the vast majority of cases the one disease develops during the decline of the other. We have never seen measles in its early eruptive

FIG. 118.—Measles in an adult, resembling smallpox.

stage complicated by a second infectious disease. Measles and whooping cough seem to succeed each with more frequency than any other disease. Among 166 cases of measles Bernardy[1] saw pertussis develop in 21 instances.

THE PATHOLOGY OF MEASLES.

Skin.—At autopsy the eruption of measles is not visible unless there has been hemic extravasation into the skin.

The skin has been studied histologically by Neumann, Catrin and Unna. Neumann[2] found as the chief changes a round-cell infiltration about the bloodvessels, hair follicles and sweat glands. Catrin[3] like-

[1] Ann. Gynec. and Pediat., July, 1894.

[2] Histolog. Veränderungen der Haut. bei Masern u. Scharlach, Med. Jahrb., 1882, p. 159.

[3] Les alterations de la peau dans la rougeole, Arch. d. méd. exper., 1891, No. 2; quoted by Unna.

wise observed a pronounced infiltration of leukocytes, but in addition, in the nodular form of measles, a series of changes in the deep epidermal cells. These consisted of a colloid degeneration of the perinuclear zone of some of the deep-lying epithelial cells. Around the areas of colloid change were dilated interepithelial spaces containing coagulated fibrin and leukocytes. In the center of the papule the colloid masses run together and undergo coagulation necrosis, this taking place in the prickle layer.

Catrin only found emigration of leukocytes from the papillary blood-vessels at those places where the surface epithelium contained colloid cells. Unna regards the colloid change and necrosis of the epithelium as the result of the direct influence of the poison of the disease upon the epidermal structures.

Unna[1] states that in measles a spastic resistance in the cutaneous vessels is added to the primary congestive hyperemia which develops around the infection in the capillaries, and this explains the cyanotic color, the papular swelling and the urticarial edema of the center, as well as the frequent escape of coloring matter of the blood. The rapidly developing spastic edema always collects at the place of least resistance, which, in children, is in the fatty tissue around the coil glands and in the sheaths of the larger vessels, the cutaneous muscles and follicles. The individual coils, the hair follicles and the muscles seem to swim free in widely dilated spaces.

Dilated lymph vessels and enormously distended lymph spaces are seen in the lower and central parts of the cutis. Another characteristic is the almost complete absence of a cellular exudate. Leukocytic emigration is not more than in all simple stagnatory hyperemias, less, indeed, than in most. But a few leukocytes are found in the epithelium. During the stage of scaling the subbasal horny layer separates itself from the basal and, with the central and upper horny layers, form the scale. The lost epithelium is replaced, as usual, by mitotic proliferation. The above description, Unna remarks, refers merely to the ordinary flat or slightly papular eruption.

Mucous Membranes.—The mucous membrane, of the nose, mouth, pharynx, larynx, trachea and bronchi is the seat of a catarrhal inflammation. The epithelial cells undergo a colloid change and are often swollen and detached. The lymph follicles and the surrounding structures are infiltrated with cells. Occasionally when the inflammation is intense the follicles may break down and form ulcers. At times such ulceration in the larynx may lead to involvement of the cartilage. Slawyk,[2] in a histological study of the oral mucous membrane, found the epithelium thickened and in places undergoing fatty degeneration, giving rise to the whitish dots described by Koplik.

Steiner[3] observed in several cases, at autopsy, a blotchy redness of

[1] Histopathology of the Skin, translated by Dr. Norman Walker, 1900.
[2] Quoted by Corlett: Deutsch. med. Wchnschr., April 28, 1898.
[3] Quoted by Thomas: Loc. cit., American edition, p. 72.

the mucous membrane of the larynx and bronchi, and Wilson, Eisenmann, Rayer and Gerhardt saw a similar condition in the trachea and bronchi.

Heyfelder,[1] one of the older writers, describes an eruption similar to that on the skin in the duodenum, jejunum and, at times, in the stomach and ileum; this has been noted also by several other observers. More recently Steiner[2] mentions a blotchy redness of the intestinal mucous membrane occurring in children dying during the eruptive stage.

According to Worthington,[3] the lymphatic follicles and Peyer's patches of the bowel may undergo destructive ulceration, leading even to perforation. Thomas says that Fuchs saw, upon the genital mucous membrane, numerous red, somewhat puffy spots overspread with mucus. This observation was likewise made by Henoch and Chomel.

Lymphatic Glands.—The lymphatic glands are enlarged in measles, but to a less extent than in scarlet fever. When bronchopneumonia is present the tracheo-bronchial glands may be found distinctly swollen. In a certain proportion of cases the glands show evidences of tuberculosis. Loomis, Pizzini and Kalbe[4] found tubercle bacilli in apparently normal tracheo-bronchial glands; the last-named observer noted the presence of these bacilli in 8 per cent of apparently healthy glands. It is suggested that these lie dormant until an attack of measles or some other affection involving these glands stimulates the tuberculous process to activity.

Lungs.—Bronchopneumonia is present in a large proportion of the fatal cases. The process is not essentially different from that observed in bronchopneumonia independent of measles save that there is a more pronounced tendency in many cases to suppuration. It is not rare for the pulmonary trouble to eventuate in tuberculosis, exhibiting usually in form of a caseous pneumonia.

Cornil and Babes[5] have described a peripneumonia which occurs early in the so-called suffocative cases and which they regard as peculiar to measles. It begins in the lymphatic tissue, involves the interlobular and interalveolar structures, and leads to fibrinous exudation into the air vesicles.

Stiebel[6] speaks of a blotchy redness of the pleural membranes which he observed in 4 autopsies. They were sharply contoured, red spots, apparently situated just beneath the pleura on both sides.

Roger observed a purulent pleurisy during convalescence from measles in a child five years of age.

Spleen.—The spleen is moderately swollen in measles, although this is more often determined at autopsy than at the bedside.

Liver.—Freeman[7] found focal necrosis of the liver in 4 out of 14 autopsies on measles cases. The larger areas of necrosis are visible to

[1] Quoted by Thomas.
[2] Ibid.
[3] Quoted by Dawson Williams.
[4] Mentioned by Roger: Loc. cit., p. 1004.
[5] Quoted by Williams: Loc. cit.
[6] Quoted by Thomas: Loc. cit.
[7] Result of Work at the New York Foundling Asylum, Arch. Pediat., February, 1900, and New York Med. Rec., 1898, vol. **54**.

the naked eye and may be confounded with tubercle. Microscopically there is a sharply circumscribed roundish area of necrosis in which the cytoplasm fails to stain, and fragmentation of the nuclei is seen. The condition is due to the local action of bacterial toxins.

Blood.—In uncomplicated cases of measles the condition of the blood is unaltered. The number of *erythrocytes* is not strikingly reduced in mild or moderate cases, and may at times be actually increased. In 8 cases Felsenthal counted from 5,000,000 to 5,500,000 corpuscles. The hemoglobin is likewise slightly or not at all reduced.

The *leukocytes* not only are not increased in measles, but they are often reduced below the normal. In 8 cases Rieder noted an average of 7500 cells, the leukocytes being least numerous at the height of the disease and increasing as the fever disappeared. Cabot[1] states that during convalescence the lymphocytes and especially the large mononuclear forms are increased.

According to Coombe, uniform changes occur in the blood in the incubation period. Coombe[2] says: "In the incubation period of measles there is a hyperleukocytosis without other symptoms. This is a constant sign of the incubation period. During the last two days of the period of invasion or exanthem, and throughout the entire period of the exanthem, there is a *hypoleukocytosis*." This initial leukopenia is sometimes followed by a mild leukocytosis.

These alterations are due to the change in the number of the polymorphonuclear neutrophiles. These observations were confirmed by Platenga,[3] who also found similar changes in rubella. During convalescence a mild lymphocytosis may be observed.

The eosinophile cells are usually decreased or normal in number. Cabot found the differential counts normal; Felsenthal found the polymorphonuclear cells much increased and eosinophiles never over 1 per cent. Bunting and Thewlis,[4] however, have observed a moderate eosinophilia in some cases.

In cases in which the *diagnosis* between scarlet fever and measles is obscure a differential blood count should be of distinct value. On the other hand, the examination of the blood is of no particular value in differentiating measles from rubella (rötheln), inasmuch as the cellular constituents are much the same in the two diseases.

THE DIAGNOSIS OF MEASLES.

It is a matter of great importance, particularly in institutions for children, that the diagnosis of measles be made at as early a date as possible in order that the spread of the infection may be prevented. Unfortunately the contagium of measles is transmitted at a very early period, not infrequently on the first and second day of the invasive

[1] Clinical Examination of the Blood, 4th ed., New York, 1901.
[2] Arch. de méd. des enfants, 1903.
[3] Ibid., March, 1903.
[4] Arch. Path. and Lab. Med., 1926, **1**, 189.

illness and before the diagnosis is firmly established. The existence of an epidemic of measles or knowledge of exposure to the disease will put the physician on guard and often enable him to make a diagnosis, or at least strongly suspect it, upon the first development of catarrhal symptoms. The statement is equally true of measles and smallpox, that the diagnosis cannot be indubitably made before the appearance of the eruption, although when all of the invasive symptoms are typically developed, when there has been exposure to the disease, and particularly when the characteristic buccal enanthem is present the diagnostic probability approaches almost to a certainty. As in smallpox, the vaccinal condition of the patient often constitutes information of important diagnostic value, so in measles does the history as to previous attacks. It is generally agreed that second attacks of measles are of great rarity. In a doubtful case an authentic history of a previous attack of measles would constitute strong presumptive evidence against the rubeolous nature of the disease under consideration.

While the diagnosis of measles is usually announced when the eruption appears, it must not be thought that the rash is in itself all-sufficient evidence.

The eruption of measles is merely its most conspicuous manifestation. Rashes indistinguishable from the measles exanthem may, at times, appear in other diseases. The diagnosis is to be made by attention to the history, the catarrhal symptoms, the fever and the eruption, both upon the skin and buccal mucous membrane. A due sense of proportion must be cultivated so that the presence or absence of certain symptoms may be accorded its proper value.

Ordinarily the diagnosis of measles presents no difficulties. When, however, the disease appears in unusual guise, in extremely mild or malignant or irregular form, the determination of the nature of the disease may be most perplexing. Especially is this true in those rare cases of *measles without eruption;* in such instances the diagnosis can only be made when the history and the entire clinical picture, save the eruption, bespeak measles.

Diagnostic Value of the Enanthem or Mucous-membrane Eruption (Koplik's Spots).—It is stated by Northrup[1] that the typical buccal spots are present in measles in about 91 per cent of cases, that they are seen only in measles and that they ordinarily appear from one to three days before the cutaneous eruption.

Our own experience would confirm this statement. We have observed the spots as early as three days before the appearance of the cutaneous exanthem. We have never seen these spots in rubella, scarlatina or any other disease save measles.

Rotch, of Boston, reflects the general opinion in the following statement: "The presence of Koplik's spots helps in a large majority of cases. The consensus of medical opinion appears to be that, while

[1] Von Jürgensen: Measles, Nothnagel's Encyclopedia of Practical Medicine, American edition; additions by Northrup.

their absence does not exclude measles, their presence is pathognomonic of measles."

Sevestre[1] insists upon the diagnostic importance of the erythema of the soft palate which precedes by one or two days the exanthem of measles. "The redness is not uniform, but presents itself in the form of small, rounded or irregular spots, which are sometimes disseminated in small number and at other times almost confluent." This appearance of the soft palate, to our minds, is scarcely sufficiently peculiar to measles to be of much diagnostic value.

It is at times a matter of importance to determine during convalescence the nature of the preceding disease. Measles may often be diagnosed by the brownish-red stains on the body as late as a week or ten days after the subsidence of the eruption. Inasmuch as children in this condition may be capable of transmitting the infection, it is important in schools, asylums or other institutions for children to exclude or isolate such patients. Not infrequently a mild grade of blepharitis persists after an attack of measles.

Rubella (**Rötheln**).—This affection is more apt to be confounded with measles than any other. Confusion may arise when measles presents itself in very mild form or when rubella appears, as it sometimes does, with severe manifestations. The history as to the previous occurrence in the patient of the one or the other disease is evidence of considerable importance. It is uncommon for measles to attack an individual twice and still rarer for rubella to act in this manner.

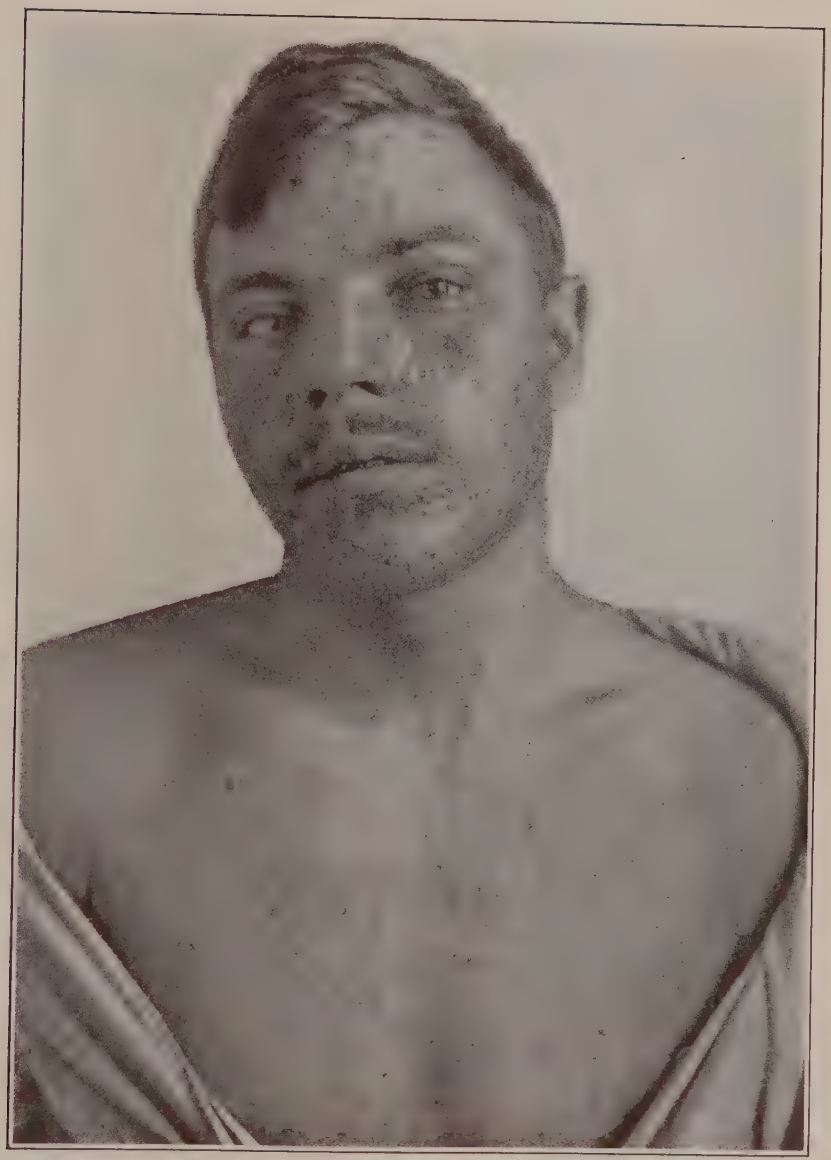
The prodromal stage in rubella is very brief, rarely lasting more than twenty-four hours; the catarrhal symptoms are slight or absent. It will be helpful to remember that catarrhal manifestations are more pronounced in mild cases of measles than in severe cases of rubella. The characteristic buccal spots seen in measles are absent in rubella. The fever is slight, commonly 99° or 100° F., and rarely exceeding 101° F.; it is of short duration. The eruption in rubella spreads more rapidly than in measles and is of briefer duration. The lesions are slightly elevated macules, of a pale rose-red color and pin-head to pea-sized. The eruptive elements are smaller, paler and more discrete than in measles. The patient with rubella often feels well enough to remain out of bed. A more exhaustive differential diagnosis is given in the chapter on Rubella.

Scarlet Fever.—It is only in anomalous cases that scarlatina is apt to be confounded with measles; ordinarily the differentiation of these affections is a simple matter.

In scarlatina the onset is more stormy, with high fever and a much greater tendency to vomiting. The eruption usually comes out on the second day, earlier therefore than that of measles. Photophobia, coryza, hoarseness and cough are lacking in scarlatina, but instead we find sore throat, marked glandular enlargement about the jaws and a

[1] Quoted by Comby: Loc. cit., p. 195.

PLATE XIX



Measles with Papular Lesions, sent into the Philadelphia Hospital for Contagious Diseases as a Case of Smallpox

characteristic tongue. The peculiar buccal spots of measles are absent, the oral and pharyngeal mucous membrane showing merely congestion. The face is less intensely involved by the rash than in measles and, moreover, shows circumoral pallor.

The rash in scarlet fever is diffuse and punctiform; it should be remembered, however, that on the arms and legs it is not infrequently blotchy and suggestive of measles. The subsequent desquamation is more profuse and lamellar in character. Otitis media and albuminuria are common complications. In septic cases purulent nasal discharge is not uncommon even in the early stages of the disease; laryngeal symptoms are, however, rare.

Confusion may result in those cases of measles in which there is a tendency to general confluence of the rash; usually some portions of the cutaneous surface will exhibit the measly character of the rash. In patients seen late brownish stains on the body speak for measles, and pronounced desquamation on the hands and feet and albuminuria point toward an antecedent scarlet fever. The leukocytic count is a test of great value, a leukocytosis being present in scarlet fever but not in uncomplicated measles.

Influenza.—"La grippe," particularly that form accompanied by catarrhal inflammation of the upper air passages, may present a considerable resemblance to measles during the invasive stage. It is manifest that a disease beginning with fever, coryza and cough might readily be either measles or influenza. Photophobia, which is justly regarded as a significant symptom by the laity, is usually well marked in measles and absent in influenza. If the characteristic bluish-red spots with whitish specks on their summits be visible upon the buccal mucous membrane the diagnosis is at once made clear.

The presence of an epidemic of one or the other disease will often aid one in early arriving at a correct diagnosis.

Smallpox.—During epidemics of smallpox, cases of measles are not infrequently confounded with variola. We have had numerous cases of measles sent into the Philadelphia Hospital for Contagious Diseases under the diagnosis of smallpox. On the other hand, the reverse error is by no means rarely made. It is particularly the severe cases of smallpox with considerable turgescence of the skin that simulate measles. Standing some feet from the patient the resemblance in these cases is striking. Some cases of measles are accompanied by a considerable degree of papulation; when such an eruption is developed by an adult during an epidemic of smallpox, an error might at the very beginning be readily made (Fig. 119). A further point of resemblance is that each disease is preceded by a prodromal stage of almost the same duration.

The constitutional symptoms preceding smallpox are, however, usually more severe (temperature 104° to 105° F.) and are commonly, though not always, accompanied by pronounced backache. The temperature, moreover, falls a few days after the appearance of the erup-

tion, while the fever in measles continues high during the eruptive stage.

The catarrhal symptoms affecting the eyes and respiratory passages, which are so constant in measles, are absent in smallpox, at least during the prodromal stage. Close inspection of the mouth in smallpox may reveal the presence upon the soft palate of rounded, glistening, pin-head-sized, reddish elevations, but these differ considerably from the bluish-red spots on the buccal mucous membrane in measles.

FIG. 119.—Smallpox on the second day of the eruption, presenting some resemblance to the eruption of measles.

The maculo-papules of measles are soft and velvety to the touch, as compared with the firm, shotty character of the smallpox papules. The sweep of an experienced hand over the skin will often suffice to differentiate the two diseases. Where there is doubt twenty-four hours' delay will dispel all uncertainty, for by this time the eruption of measles will have become flatter and more diffuse, and the papules of smallpox firmer and more distinctly elevated.

The prodromal morbilliform rash, the so-called *roseola variolosa*, may be confounded with measles. This eruption occasionally develops in mild cases on the second day of the invasive stage. The lesions are non-elevated, irregular in distribution, of brief duration and unaccompanied by catarrhal symptoms.

Typhus Fever.—During the epidemic prevalence of typhus a confounding of this disease with measles might take place when the eruption is profuse. Pastau is quoted by Thomas as saying that the exanthem of typhus is by no means rarely papular or even hemorrhagic like that of measles, and a catarrhal affection of the air passages, especially of the trachea, is one of its usual concomitant symptoms. The fever and nervous symptoms are more pronounced in typhus and there is great enlargement of the spleen; the eruption is usually absent on the face, and oculo-nasal catarrh is lacking. We recall a case of atypical measles which was sent to the Philadelphia Hospital for Contagious Diseases as a case of typhus by one of the foremost physicians of this country.

Roseola Syphilitica.—The macular eruption of syphilis has on more than one occasion been confounded with measles. The error of mistaking syphilis for measles may be made when the patient is an adult and when the febrile symptoms are mild. On the other hand, syphilis with pyrexial elevation might be confused with measles.

The eruption of syphilis is slower in development and the lesions are much more uniform in size and distribution. The face is but slightly, if at all, involved. Usually the initial lesion or the hardened remains thereof can still be discovered. In addition, other evidence of the syphilitic infection may be present, such as mucous patches, pronounced inguinal adenopathy, etc.

Morbilliform Erythemata.—There are a number of conditions in which rashes bearing a more or less close resemblance to that of measles may occur. They may be divided into: (*a*) Accidental rashes accompanying the exanthematous fevers, (*b*) drug eruptions, and (*c*) serum eruptions.

Mention has already been made of the resemblance of the roseola variolosa to measles. An analogous eruption, *roseola vaccinosa*, develops occasionally about the tenth day of vaccination. The same features which have been referred to as distinguishing the variolous roseola from measles may be applied to the vaccinal rash. Morbilliform rashes may in rare instances be observed also in the course of varicella, scarlet fever and other infectious diseases.

Drug Eruptions.—The drugs which most frequently give rise to eruptions simulating measles are antipyrin, luminal and other drugs of this series, quinine, chloral, copaiba and cubebs.

The most common eruption resulting from the administration of *antipyrin* is a morbilliform erythema. Of 52 instances of eruption from the use of antipyrin collected by Spitz, 41 were of the measles type. The eruption may be generally distributed over the trunk and extremities or it may be limited to certain regions thereof; an important distinguishing feature is that the face is usually exempted. Crocker states that these eruptions may be accompanied by oro-nasal catarrh. The difficulty in diagnosis may be increased by the appearance of the antipyrin eruption following catarrhal symptoms, such, for instance, as are encountered in influenza, for which the drug is administered. The conjunctivitis, photophobia, hoarseness, cough and buccal eruption are all absent. Fever, when present, is slight and not characteristic of measles. Furthermore, the normal progression of the measles exanthem from the face and neck gradually downward will be found lacking. The eruption, moreover, is apt to be non-elevated and exhibit irregularities as to distribution. If a large dose of antipyrin has been taken, the drug can be found in the urine by testing the same with the perchloride of iron.

Quinine.—Quinine gives rise not infrequently to erythematous eruptions. Of 60 quinine eruptions analyzed by Morrow, 38 were of the erythematous variety. Most of these are of the scarlatiniform type, but some resemble measles. The rash may develop after the administration of as small a quantity as a grain or even a fraction of a grain of the drug. The idiosyncrasy appears to be most frequently observed in women.

The eruption may be generally distributed or limited to certain areas.

It sometimes appears first on the face, spreading thence downward over the trunk and limbs. The lesions are bright or dull red macules or papules, which may quite strongly resemble the measles exanthem. Itching is apt to be a more prominent symptom than that accompanying measles. Desquamation not infrequently follows. In some cases febrile symptoms are present at the beginning; there may be a fever of 101° or 102° F., with headache, nausea or vomiting and weakness. Catarrhal symptoms are absent.

Eruptions from the administration of *chloral* are less common than those after antipyrin or quinine. Gee[1] saw 2 cases in which there was a dusky-red, papular eruption surrounded by a more diffuse redness of the face and neck, and patchy or mottled-red spots on the extremities, especially about the articulations.

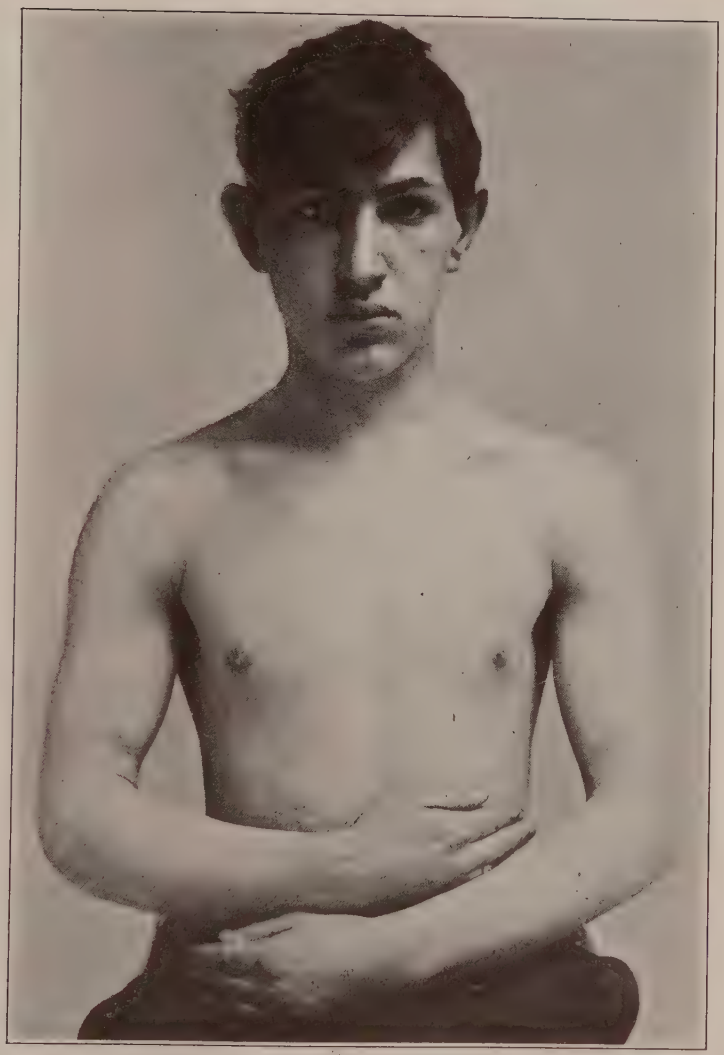
The absence of the catarrhal and constitutional manifestations of measles would enable one to exclude this infection.

Fig. 120.—Copaiba eruption resembling measles.

Copaiba and Cubebs.—Copaiba and cubebs may give rise to scarlatiniform or morbilliform rashes. The former drug usually produces an

[1] Quoted by Crocker: Diseases of the Skin, American edition, 1903, p. 483.

PLATE XX



Copaiba Eruption Resembling Measles.

eruption consisting of rose-red colored, slightly raised patches, which may be discrete or blotchy and generalized or limited. About the elbows and knees there is a tendency toward confluence of the patches. Itching is apt to be a distressing symptom. The eruption may develop rapidly after the administration of the drugs or only after some days have elapsed. Most of the eruptions have occurred in persons who were receiving treatment for urethritis. A peculiar and disagreeable balsamic odor is often imparted to the skin when copaiba is taken.

One of the writers has seen 2 cases of severe morbilliform eruption associated with blebs, with intense injection of the conjunctivæ and moderate fever, 1 of which was diagnosed by the physician in attendance as measles. The patients were taking luminal.

All of the drug eruptions are apt to exhibit irregularities as to the manner, rapidity, distribution or duration of the eruption which will arouse suspicion as to its nature; furthermore, the prodromal stage of measles with its characteristic catarrhal symptoms is wanting.

Antitoxic Sera.—Antitoxic sera occasionally call forth eruptions which are measles-like in character. Diphtheria antitoxin may now and then give rise to a morbilliform erythema, although much more commonly the eruption resembles urticaria or exudative erythema. Antitoxin rashes may develop at any time from three days to three weeks after its administration; most rashes, however, appear from eight to fourteen days thereafter. There may be elevation of temperature with joint pains and occasionally joint swellings accompanying the eruption. The temperature may rise suddenly to 102° F. or thereabouts but it soon falls. Catarrhal symptoms are invariably absent.

The antistreptococcus serum and antitetanic serum may, on rare occasions, also give rise to morbilliform eruptions.

THE PROGNOSIS OF MEASLES.

It appears to be a difficult matter to dispel from the minds of mothers the idea that measles is a trivial disease. When it is stated, according to the *Twelfth Census Report*, that measles in the United States, in the year 1900, causes 12,866 deaths, more than twice the number that resulted from scarlatina, it is evident that this disease is not essentially benign in its outcome.

The prognosis of measles in vigorous and well-nourished children beyond the age of two or three years is extremely favorable.

The factors that exert an important influence upon the prognosis are the age of the patient, his previous health and the nature of his surroundings. Season and climate are thought to exercise some influence upon the disease and its complications.

Age.—The age of the patient is the most important factor in estimating the degree of danger attendant upon an attack of measles. During the first six months of life infants usually resist the infection of measles altogether or take it in feeble form. With this exception,

children under two years of age who contract measles have a dangerous disease to contend with. Holt states that the average mortality from measles during this period is not far from 20 per cent.

After the third year of life the danger rapidly diminishes, reaching a minimum after the age of five has been passed.

Dawson Williams states that in the forty years from 1848 to 1887 there were in England and Wales 367,602 deaths attributed to measles, and of this number, 335,874 occurred in children under five years of age, leaving only 31,728 to distribute among other ages.

The best opportunity of judging of measles susceptibility and fatality at the various ages is afforded in studying an entire epidemic in a locality. Dr. Theodore Thomson[1] presents such a table of an epidemic in an English town, from which the following data are abstracted:

Age.	Population.	Measles attacks.	Deaths.	Mortality-rate, per cent.
0 to 1 year	1,155	166	16	6.9
1 to 2 years	974	233	46	23.6
2 to 3 "	1,028	354	36	17.5
3 to 4 "	1,000	324	16	8.0
4 to 5 "	951	324	5	2.6
5 to 10 "	4,530	560	6	0.7
10 years and upward	25,968	39	0	0.0
At all ages	35,606	1031	125	1.7

This table indicates the lesser susceptibility of infants under one year of age and also the lower death-rate as compared with the next two years.

During youth and early adult life the mortality from measles is low. Patients who are advanced in years not infrequently succumb to the disease. This is shown in Panum's[2] report of the Faroe Islands epidemic of 1845.

Mortality-rate of Measles in the Faroe Islands in 1845.

Age.	Mortality-rate, per cent.	Age.	Mortality-rate, Per cent.
Under 1 year	30.00	40 to 50 years	2.8
1 to 10 years	0.60	50 to 60 "	4.5
10 to 20 "	0.40	60 to 70 "	7.8
20 to 30 "	0.75	70 to 80 "	13.1
30 to 40 "	2.10	80 to 100 "	26.1

These figures are unusual, in that such a great mortality is shown in infants under one year of age and such a remarkably small death-rate in those between one and three years. The increasing mortality in patients past the age of forty years is well illustrated. In an extremely mild epidemic in the Faroe Islands, in 1875, Hoff states that while

[1] Quoted by Williams: Loc. cit.
[2] Loc. cit., p. 287.

only 8 out of 1123 cases ended fatally, 5 of these were vigorous adults between the age of twenty and thirty years. This must be regarded as an exceptional circumstance.

Institutional Epidemics.—It will be found convenient to discuss here the influence of institutional environment upon the mortality-rate of measles. It is a generally recognized fact that measles occurring among children in homes, nurseries, asylums, hospitals, etc., is much more fatal than when it develops among children in their private homes. Indeed, measles is regarded as the scourge of children's institutions, for it decimates the little patients like a plague. There are a number of reasons for this. Such children usually come from poor stock and therefore lack power of resistance. The children in foundling asylums, nurseries and hospitals are of a tender age, which in itself accounts for a high mortality. They are usually frail and in poor health or already perhaps suffering from an acute or a chronic disease. The atmosphere is often vitiated and infected, and the liability to such complications as pneumonia and diphtheria is increased.

The mortality in such institutions as have been mentioned is often frightful. Holt speaks of an epidemic in 1892 in the Nursery and Child's Hospital in New York in which there were 143 cases with a death-rate of 35 per cent. An epidemic in the same institution in 1895 had an almost identical mortality-rate.

Comby gives the following statistics showing the death-rate in some of the Paris hospitals:

HÔSPICE DES ENFANTS ASSISTÉS.

Year.	Cases.	Deaths.	Percentage.
1882	280	128	45.00
1883	268	128	45.00
1884	328	187	57.00
1885	370	147	46.00
1886	329	138	42.00
Total in five years	1575	728	46.22

The death-rate, therefore, during these five years was nearly 50 per cent, a truly appalling figure.

In l'Hôpital des Enfants Malades, for a period of seven years, from 1882 to 1888, there were treated 2585 cases of measles, with a death-rate of 40.15 per cent.

In l'Hôpital Trousseau, from 1882 to 1886, there were 907 cases of measles, with a mortality-rate of 25.02 per cent. From 1890 to 1894 there were 2248 cases treated in special isolation pavilions, but the mortality-rate still remained high—28 per cent.

It is difficult to obtain accurate information as to the death-rate of measles in private practice, for while the deaths are recorded the number of attacks is usually not known. The fact is well established, however, that the fatality is very much less in this class of patients.

Sex.—Sex does not influence the mortality from measles. Of 12,866 persons who died of measles in the United States in 1900, 6231 were males and 6635 were females. The frequency of measles in pregnant women is not sufficient to disturb the balance. Moreover, the infection of measles superadded to pregnancy is not as serious as some of the other exanthematous diseases, notably scarlet fever and smallpox.

Previous Health of the Patient.—Measles as a primary disease is very much less serious than when it becomes engrafted upon some other acute or chronic affection. Secondary measles is an extremely fatal disease; occurring in patients who are convalescing from diphtheria, scarlet fever, whooping cough, etc., the danger is greatly enhanced.

The mortality is also high when measles attacks children who are badly nourished and who are scrofulous or anemic. In those with enlarged glands and a tendency to pulmonary tuberculosis an attack of measles may be sufficient to stimulate this process into activity. The unfavorable influence of hardship and privation is exemplified in camp measles, which is nearly always characterized by a high death-rate.

Character of Epidemic.—The mortality of measles depends much upon the severity of the prevailing epidemic. At times the type of measles is unusually mild and the death-rate extremely low; some epidemics, on the other hand, are characterized by special malignancy. Fatal epidemics of measles may cause a high mortality, not only through an excessive development of the regular symptoms of the disease, but through the frequency of serious complications. Indeed, it is the frequency or rarity of bronchopneumonia during an epidemic that determines in a large measure its malignancy.

The average mortality of measles is from 4 to 6 per cent. The deaths may in some epidemics not exceed 1 or 2 per cent, while in others they may reach the murderous figures of 20 or 30 per cent.

In 1856, in Lippe, Hungary, a malignant epidemic prevailed, destroying the lives of 50 per cent of those attacked. Measles again occurred in this locality thirteen years later, with a mortality of 3 per cent.

Faber states that at Schorndorf in the epidemic of 1827–1828 there were 2100 cases of measles, with a mortality of only 1.8 per cent. Among other mild epidemics may be mentioned the following, quoted by Thomas: According to Ranke, the mortality in four epidemics in Munich varied from 0.7 to 2.7 per cent. Kostlin reports a mortality in Stuttgart of 1.8 per cent for the years 1852 to 1865.

Among severe epidemics (according to Thomas) may be mentioned the fatal epidemic in the district of Zolkiew in 1840; Seidl mentions that out of 1519 cases there were 196 deaths, a mortality of almost 13 per cent. According to Schüz, measles prevailed at Nagold with a mortality of 10 per cent. Small epidemics in certain localities have been accompanied by even higher mortality.

Colin[1] gives the following figures:

Year.	Localities.	Cases.	Deaths.	Percentage.
1861	Ruelle	582	139	27.7
1864	Arras	45	13	28.8
1860	Val-de-Grace	125	40	32.0
1870	Bicetre	457	168	36.7

A malignant epidemic raged in Sunderland, England, in 1885. Harris[2] states that of 1316 cases, 384 died, giving a mortality of 29 per cent.

Measles often manifests unusual malignancy on reaching a virgin soil, particularly among savage tribes. It is stated on the authority of d'Alves that 30,000 Indians perished from measles along the banks of the Amazon River in 1749–1750. In 1806, in Madagascar, 5000 persons are said to have succumbed to the disease in a single month. Among the Fiji Islanders measles has exhibited as high a death-rate as 30 per cent; the disease has, as might be expected, inspired a wholesome dread among the natives.

Measles in Army Camps 1917–1918.—During the winter of 1917–1918 there were sixty-two times as many cases of measles at Camp Pike, where the division consisted of recruits from the southern states, as there were at Camp Upton, where the soldiers were nearly all drafted from New York City. In nearly all camps the extent of measles was proportionate to the number of rural recruits in the said camps.

The Surgeon-General's report for 1918 reported 48,900 cases of measles in the army, with 2075 pneumonia following the same.

Season and Climate.—Inasmuch as the mortality of measles is greatly influenced by the frequency of pneumonia, one would naturally suppose that this complication would be more common and the death-rate consequently higher in the cold and inclement seasons of the year. But such an assumption is not entirely borne out by facts. The figures which are published by writers as to the influence of season on measles mortality lack uniformity and preclude the possibility of drawing therefrom satisfactory conclusions.

Deaths from Measles in England and Wales by Quarterly Periods.

Quarterly periods.	1837.	1838.	1839.	1840.
January, February and March	..	2022	2,074	2836
April, May, June	..	1512	3,204	2641
July, August, September	2362	1037	2,767	1739
October, November, December	2392	1943	2,892	2110
Total deaths	4754	6514	10,937	9326

Gregory, who publishes the above table, remarks that "Season would appear to have less influence on the mortality of measles than might have been anticipated."

[1] Quoted by Comby.

[2] Lancet, April 30, 1887, p. 970.

According to Karajan,[1] measles occurring in lower Austria in 1862, during the presumably unfavorable cool months, was attended with a mortality of only 2.29 per cent, whereas the disease prevailed in the same district during the following summer with a mortality which reached 6.29 per cent.

Passow[2] states that the fatal cases of measles in Berlin from 1863 to 1867 were distributed as follows: winter, 41.4 per cent; autumn, 33.4 per cent; summer, 13.3 per cent; spring, 11.9 per cent.

In the United States the most fatal season from measles would appear to be the late winter and early spring months.

In New York City, during a period of fifteen years, from 1830 to 1844, in which time 2104 deaths from measles occurred, the seasonal mortality was as follows:

	Deaths.
January, February, March	610
April, May, June	574
July, August, September	536
October, November, December	384

It is thus seen that the highest mortality was in the first three months of the year and the lowest in the last three.

The *United States Census Report* for the year 1900 shows that the greatest number of deaths from measles occurred during the months of February, March, April and May.

Climate doubtless has some influence upon the mortality of measles. Gregory says that "In hot countries measles is not viewed with alarm, evidently from the absence of thoracic complications." It occurs to us, however, that the greater tendency to intestinal complications might counterbalance the advantage. The mortality of measles varies in different localities. It is, as would be expected, greater in large cities, where there are greater numbers of overcrowded poor than in rural districts. Even in large capitals a considerable discrepancy in the mortality exists.

Thus the mortality from measles is much greater in London than in Berlin; this is strikingly shown by the following figures:

MEASLES DEATHS PER 10,000 POPULATION.

Year.	Paris.	London.	Berlin.	Vienna.
1880 to 1889	52	60	30	
1890 to 1894	41	77	20	70
1895	26	59	17	49

From a consideration of the above remarks, it will be seen that many factors influence the prognosis; chief among these, however, are the age of the patient, his general health and environment and the severity of the epidemic. Those epidemics which furnish the largest number of anomalous cases and the greatest percentage of serious complications are most to be feared.

[1] Quoted by Thomas. [2] Ibid.

Bronchopneumonia causes 9 out of 10 deaths from measles. It is the principal danger to which measles patients are liable. Holt states that of 51 fatal cases of measles, 45 were due to bronchopneumonia, 4 succumbed to ileo-colitis and 2 to membranous laryngitis.

Among 36 deaths observed by Northrup,[1] in an epidemic in the New York Foundling Hospital, bronchopneumonia was found *postmortem* in 31 cases.

The mortality-rate today of scarlet fever is considerably lower than that of measles. During the year 1927 the mortality-rate of scarlet fever in the Philadelphia Hospital for Contagious Diseases was only 0.68 per cent. The death-rate from measles in the United States is well shown in the following table:

DEATH-RATE FROM MEASLES PER 100,000 POPULATION IN REGISTRATION AREA OF UNITED STATES.

Year.	Death-rate.	Year.	Death-rate.
1900	12.5	1915	5.4
1910	12.3	1916	11.1
1911	10.0	1917	14.3
1912	7.0	1918	10.8
1913	12.8	1919	3.9
1914	6.8	1920	8.8

Favorable Symptoms.—The symptoms of measles are favorable when the initial temperature is moderate, not exceeding 103° F., and when it remits in the preëruptive stage; when the temperature declines with the beginning fading of the eruption; when the eruption is discrete, well developed and of bright color; when it appears about the fourth day and progresses gradually over the body; when the catarrhal symptoms are of moderate intensity; when complications are absent.

Unfavorable Symptoms.—It is unfavorable for the initial temperature to be very high (above 103° F.), or for it to persist high or increase before the eruption appears. It is ominous for the fever to remain high after the rash fades, for this usually portends pulmonary complications. It is unfavorable for the eruption to appear late, for it to be unusually profuse or confluent or, on the other hand, sparse, pale and livid. A partial or poorly developed eruption with high fever is a bad sign. Hemorrhagic eruptions are usually of evil portent, especially when accompanied by hemorrhages from the mucous membranes. Sudden and premature recession of the eruption indicates cardiac weakness. Convulsions or other marked nervous symptoms, severe diarrhea, persistent hoarseness, with difficulty in breathing or continued high temperature, indicate serious complications.

SERUM PROPHYLAXIS OF MEASLES.

Fortunately it is now proven that measles may be prevented over a period of one to two months by the subcutaneous or intramuscular injection

[1] Med. News, 1897, **71**, 817.

of serum or citrated blood from individuals who have had the disease. And owing to its high mortality among children between the ages of six months and six years, this passive immunization is well worth while and especially in institutions. In the Philadelphia Hospital for Contagious Diseases, Woody, the medical director, began using the method in 1924, and states that "During that year there were several outbreaks in the scarlet-fever wards of the hospital due to some cases of scarlet fever admitted while in the incubation period of measles. Heretofore such outbreaks have constituted the greatest menace to the safety of all the hospital's charges, and for that reason any procedure that has enabled us, even in part only, to control such a situation must be considered a life-saving measure of first-rank importance. In 1925 in the midst of the busiest scarlet-fever season the hospital has ever known, a measles outbreak of unparalleled proportions occurred in the wards. To combat the situation with convalescent serum was entirely out of the question, so we, therefore, turned to adult whole blood, 1 or 2 ounces, taken from a parent and injected into the thigh muscles of the patient. By the use of convalescent serum and parental whole blood, measles as a crossed-infection has been robbed of its terrors. In the way of crossed-infection prevention in a contagious disease hospital, the use of convalescent measles serum and parental whole blood are considered the most effective measures." With this method Woody has observed the following results:

Of 96 non-immune children—

35 were immunized one day after one exposure.
17 were immunized 4 days after one exposure.
44 were immunized three to five days after two exposures.

Of this group only 4 developed measles.

In a second group of 26 cases—

11 were immunized one day after one exposure.
3 were immunized two days after one exposure.
12 were immunized three days after one exposure.

Of this number but 2 developed measles.

Thus among a total of 122 cases a successful immunization took place in 95 per cent. *Among those who took measles the course was favorably modified in one-half of the cases.*

Degkwitz[1] has injected 3 cc. or more of serum taken from cases of measles between the seventh and fifteenth days after the disappearance of fever, into 172 children exposed to the disease, and states that all of these escaped the disease. Richardson and Connor[2] injected 7 to 25 cc. of serum and reported that 6 were definitely exposed to measles and escaped infection; 1 control case developed measles. Eight others were partially exposed and escaped infection. In 3 others serum and nasal virus were injected simultaneously; in 2 there was no reaction, while the third developed a mild atypical rash.

[1] Ztschr. f. Kinderh., 1920, **25**, 134; 1920, **27**, 171.
[2] Jour. Am. Med. Assn., 1919, **72**, 1045.

Maggiore[1] injected susceptible children with 2 cc. of serum upon entrance into the hospital and double this amount the following day. Kutter[2] reports that of 145 susceptible children injected after the method of Degkwitz success was complete in 107 instances. Rietschel[3] also reports favorably upon this method of immunization, but draws attention to the difficulty of securing supplies of serum from young children; the serum of adults who had had measles in childhood was found less effective. Von Torday[4] inoculated 261 children with amounts of serum varying from 3.5 to 22 cc.; all had been exposed to measles and only 15 developed the disease. The short duration of the immunity is indicated by the fact that 3 of the children developed measles from seventy-two to seventy-five days later. Nicolle and Conseil[5] also report successful immunization by this method. McNeal[6] inoculated 16 children exposed to measles with 5 cc. of serum intramuscularly; of these, 4 developed the disease in a mild form.

Since then a very large and favorable literature has accumulated upon the subject, among which may be mentioned the reports of Dopter,[7] Solomon,[8] Weaver and Crooks,[9] Zingher,[10] Musser,[11] Haas and Blum,[12] Park and Freeman,[13] Debre,[14] Seligman[15] and numerous other investigators from different parts of the world.

Collection and Administration of Serum.—Blood should be removed asceptically from children with measles from the seventh to fifteenth day after the disappearance of fever and preferably from the seventh to ninth days. The children should be free of syphilis and tuberculosis. The serum is collected, cultured for sterility and preserved with 0.5 per cent phenol. The dose for immunization of children should be 10 to 20 cc. by subcutaneous or intramuscular injection. The injections should be made as soon as possible after exposure; injections made later in the period of incubation may not prove prophylactic, although apparently mitigate the severity of the attack. Reactions have not been reported, and since the serum is homologous there is no danger of anaphylaxis.

If whole blood is employed it may be taken from a recent convalescent or one who has had measles years previously, although the former is to be preferred; the technique may be any one of several simple methods as follows:

1. According as 20 or 40 cc. of blood are required, one or two 25-cc. Record syringes are sterilized, 2 cc. of 5 per cent solution of citrate placed in each, the syringe or syringes filled with blood from the donor,

[1] Pediatrica, 1921, **29**, 873.
[2] Ztschr. f. Kinderh., 1921, **30**, 90.
[3] Ibid., **29**, 127.
[4] Ibid., 148.
[5] Bull. et mém. Soc. méd. d. hôp., 1918, **42**, 336.
[6] Jour. Am. Med. Assn., 1922, **78**, 340.
[7] Paris méd., 1923, **13**, 504.
[8] Deutsch. med. Wchnschr., 1923, **49**, 1151.
[9] Jour. Am. Med. Assn., 1924, **82**, 204.
[10] Ibid., 1180.
[11] Ibid., 1927, **88**, 1126.
[12] Ibid., **87**, 558.
[13] Ibid., 556.
[14] Bull. et mém. Soc. méd. d. hôp., 1925, **49**, 682.
[15] Deutsch. med. Wchnschr., 1926, **52**, 1220.

the contents mixed and the injection given intramuscularly into the thighs or buttocks.

2. Or the required amount of citrate solution (2 cc. of a 5 per cent solution for each 20 to 25 cc. of blood) is placed in a sterile bottle, blood aspirated from a vein of the donor and expelled into the bottle. As a general rule, only one syringe is required, as it may be easily filled twice without washing between fillings, a finger closing the end of the needle to prevent bleeding while the syringe is being emptied. After the blood is secured the tourniquet is released, the syringe washed out once or twice with saline solution and the injection given.

3. Or one, two or more syringefuls of blood may be collected and expelled into a sterile bottle or flask containing glass beads, shaken for a few minutes for defibrination and the blood injected intramuscularly.

4. Or, if the patient is placed close at hand, and only 20 to 25 cc. of blood are required, a syringeful may be collected, using a gauge No. 16 or 18 needle to facilitate quick filling, the tourniquet released, needle and syringe withdrawn, and the blood injected at once (but not too rapidly) before it has had time to coagulate in the syringe.

Immunization With Animal Sera.—Tunnicliff and Hoyne[1] and Hoyne and Gasul[2] have reported favorable results with a serum which, if proved efficacious by further observation, may obviate the necessity of depending on a human supply. The serum is produced by repeated inoculations of goats with Tunnicliff's green-producing measles diplococcus and the filtrate of dextrose broth cultures of these organisms. From 4 to 6 cc. of this unconcentrated serum was injected in measles contacts. They report that most of those receiving serum within four days of exposure escaped, while little complete protection was afforded by doses giving later than this. The passive immunity produced was considered to last from two to four weeks.

Degkwitz,[3] one of the pioneers in Germany in the use of human convalescent serum, has reported good results with a serum made from the blood of sheep inoculated with the Berkefeld filtrate of the nasal secretion and sputum of measles patients early in the attack. He advocates that the serum be given between the seventh and eleventh days after exposure. This allows the development of the disease together with the production of a permanent active immunity, but converts the attack into an extremely mild one. The reports of Kaupe,[4] Noeggerath,[5] Erickson,[6] Kochmann,[7] Baron[8] and Zoepffel[9] have not been favorable.

Active Immunization Against Measles.—Active immunization of infants against measles has been attempted by Herrman.[10] In 1914 he inoculated a group of healthy babies between the age of four and five

[1] Jour. Am. Med. Assn., 1926, **87**, 2139.
[2] Ibid., 1185.
[3] München. med. Wchnschr., 1926, **181**; Klin. Wchnschr., 1926, **5**, 1361.
[4] Med. Klin., 1926, **22**, 213.
[5] Klin. Wchnschr., 1926, **5**, 1168.
[6] Med. Klin., 1926, **22**, 1332.
[7] Deutsch. med. Wchnschr., 1926, **52**, 565.
[8] Med. Klin., 1927, **23**, 48.
[9] München. med. Wchnschr., 1927, **74**, 150.
[10] Arch. Pediat., 1915, **32**, 503.

months by swabbing the fresh nasal mucus from patients just coming down with measles on the nasal mucosa of his subjects. His purpose was to introduce the virus at a time when some degree of inherited immunity would be present, but with the object of producing an active immunity. Seventy-five of his subjects have been watched from four to eight years; 62 have been directly or indirectly exposed to measles; 70 have remained free of the disease. His method, while scientifically sound, is obviously not practicable for general use.

Debra and others[1] have recently reported attempts at active immunization, using the blood of measles patients at the onset of the eruption as antigen. Children from two to four years of age were inoculated subcutaneously with 0.025 cc. of filtered blood in physiological sodium chloride solution. Slight reactions resembling those of Herrman's subjects followed in from seven to ten days. The same dosage was repeated in three weeks. The duration of the immunity thus conferred has not been determined, but the authors affirm that in most cases it persists at least several weeks. These claims are interesting, but longer observation will be required before an accurate estimate of their worth can be made.

THE TREATMENT OF MEASLES.

In discussing the treatment of measles it must be remembered that we are dealing with a disease which is far from trifling in its nature—one whose aggregate annual mortality exceeds, at the present day, that of any eruptive disease, not excluding smallpox. In 1889 there were 14,732 deaths from measles in England and Wales; in 1900 the mortality from measles in the United States was 12,866. These figures are not far from representing the average annual mortality in these countries.

We have no doubt that at least 100,000 persons, chiefly children, perish throughout the world each year from measles.

The subject is, therefore, of sufficient importance to warrant a full consideration of the *prophylactic* treatment of measles and its relation to the community at large

General Prophylaxis.—That the spread of measles can be greatly lessened by proper sanitary measures has been shown by the results accomplished by the Michigan State Board of Health.[2] Public health measures may be considered under the headings of (1) Notification, (2) Isolation and (3) Disinfection.

Notification.—There is considerable difference of opinion as to the benefits derived from making measles a notifiable disease. Bearing in mind the fact that measles in many countries kills more children than scarlet fever and diphtheria combined, there can be but one point of view as to the desirability of checking its ravages. It is only through

[1] Ann. d. méd., 1926, **20**, 343.

[2] Baker: Reports and leaflets on the Prevention and Restriction of the Infectious Diseases, etc., 1900.

a knowledge of the distribution and extent of measles that health authorities are enabled to direct measures against its spread. How effective such measures are offers latitude for discussion.

The chief difficulty arises from the early communicability of the disease. As soon as a patient manifests the first symptom of measles, those who have been exposed and are susceptible are almost sure to contract the disease, and isolation, as far as these persons are concerned, is too late. Infection may at times take place even before the patients sicken.

The *education of the masses* is a matter of paramount importance in stamping out measles. Mothers must be taught that measles is a serious disease—a disease that destroys many lives, and that exposure to it must be avoided. Even among the intelligent middle classes there is a tendency to regard escape from measles as futile, and mothers make little effort to avoid an infection which is regarded after all as inevitable. "The baby might as well take measles now as later" is the dangerous and erroneous view often expressed.

Mothers should be made to realize the fact that measles kills more children under two years of age than any other disease save possibly whooping cough, and that about 80 per cent of all deaths from measles are in children under five years of age. If children be safely guarded through this period of their life without contracting measles an enormous saving of life would result.

It is a good plan to send circulars of instruction to all households which are in the neighborhood of an infected domicile.

Isolation.—When a child is striken with measles in a household in which there are other susceptible children it should be promptly isolated. The isolation should not be delayed until the diagnosis is confirmed by the appearance of the eruption, but upon the first suspicion that the disease might be measles.

In selecting an apartment for the patient such a room or, preferably, a suite of rooms is to be chosen as can be most effectually separated from the rest of the house. It will usually be found that the uppermost rooms of the house are most suitable and available. In choosing the apartment care should be given to the facilities for ventilation. Admirable ventilation is furnished by an open fireplace in which fire is kept constantly burning, but such a convenience will usually be found wanting. The most common method of securing the necessary change of air is from a window sufficiently removed from the sick-bed to avoid direct currents of air striking the patient. A rather safer method, particularly in such a disease as measles, is to ventilate through the adjoining room, as suggested by J. P. C. Griffith.[1] The windows of this room may be kept open and the fresh air permitted to enter the sick-room through the communicating door, which is opened for this purpose from time to time. As this room also forms the channel of

[1] Hare's System of Practical Therapeutics, p. 132.

communication with the remainder of the house, the opening of the windows will tend to dilute or dissipate the infection.

All unnecessary articles of furniture, such as drapery, carpets and upholstery should be removed. The spaces around doors communicating with parts of the house to be protected should be sealed by pasting strips of wrapping paper over them. The contagium of measles is so diffusible that unless this precaution is taken the infection will travel beyond the sick-chamber. Over the door leading into the corridor should be suspended a sheet which is kept moist with diluted Labarraque's solution, carbolic acid (5 per cent), or a 1 to 1000 solution of corrosive sublimate.

The woodwork and the floors of the apartment should be kept clean by mopping with cloths saturated with antiseptic solutions. Owing to the liability to pulmonary complications in measles, sweeping of the sick-room should be assiduously avoided.

The nurse or attendant should not leave the sick-apartments save after change of clothing and thorough ablution. If the mother wait upon her child she should devote her time exclusively to the patient, and not come in contact with susceptible members of the family. Such garments should be worn by the nurse or mother as can be readily washed.

All articles coming in contact with the patient, such as dishes, bed and body linen, etc., should be disinfected in the adjoining room, where solutions for this purpose should be kept on hand. A 5 per cent solution of carbolic acid will suffice for this purpose, although for the dishes boiling water is to be preferred.

It is a difficult matter to state just how long measles patients should be isolated. Unlike scarlet fever the disease is most contagious early, and the period of infectiousness is short lived. Most pediatricians are of the opinion that the period of isolation should be in all from two to three weeks. In uncomplicated cases two weeks are probably sufficient if desquamation has ceased. Whether or not the desquamation of measles is infectious is an undetermined problem, with plenty of advocates to champion each side of the question. It is proper to state that certain physicians who have had unusual opportunities of judging, such as Hoff, Peterson and Comby,[1] deny the infectiousness of the stage of desquamation. The last-named observer says: "We know today that measles ceases to be contagious after the eruption." In institutions, where so much depends on effective isolation, patients should be separated for the full period.

Utility or Futility of Isolation.—There are many physicians who deem isolation in private residences futile and, therefore, do not advise it. It must be admitted that when measles appears in a child to whom susceptible children have been freely exposed, isolation is too late. If, however, patients are isolated upon the first suspicion of

[1] Loc. cit., p. 200.

measles a certain small proportion of the exposed will probably escape, particularly babies, whose susceptibility is slight and whom it is particularly important to protect. Where such young infants can be sent to another household this course is eminently desirable, provided no susceptible children be there resident. It is unjustifiable to send exposed children to a home where unprotected persons reside, for these in turn would be exposed upon the former falling ill.

It is, of course, recognized that the method of isolation above outlined could not be carried out among the poor nor in families living in restricted quarters. Moreover, there are many people who would refuse to go to such inconvenience and expense, with the knowledge that the benefits to be derived are doubtful. We feel that when measles breaks out in a household in which unprotected persons, particularly children under three years of age, live, the proper course to pursue is to isolate the patient. Such a procedure would, in the long run, save lives.

When measles develops in an institution for children the patient should be immediately isolated. No new admissions should be permitted save to quarters which are completely separated and protected from the infected apartments. The exposed children should be kept under close surveillance until the extreme limits of the period of incubation have been passed.

Disinfection.—The germs of measles have comparatively little tenacity to life outside of the human life. It is unusual for the disease to be carried by infected articles or third persons. We do not subscribe, however, to the positive statements made by some physicians that the disease is never communicated in this manner. In hospitals and other institutions for children wards should invariably be disinfected after measles has broken out; in private households thorough cleansing and subsequent airing may take the place of the more rigid measures of disinfection employed in other infectious diseases.

General Management of the Disease.—Measles runs its course in a definite period of time like other self-limited affections, and tends in uncomplicated cases to recovery. No known drug is able to abridge or modify the course of the disease. The therapeutic indications, therefore, are: (1) To mitigate or control excessively developed symptoms, and (2) to treat or, preferably, prevent complications.

The temperature of the sick-room should be maintained in the neighborhood of 70° F., particularly during the cold months of the year. It is important that the temperature be kept uniform and not be allowed to fall during the hours of the night. While it is desirable to avoid direct draughts upon the patient, it is equally essential to keep the room well ventilated and the air pure. Owing to the irritating influence of dry air and the increased liability to dissemination of dust in such an atmosphere, it will be found advantageous to moisten the air by one method or another. A pan of water may be heated over an alcohol lamp or the old-fashioned kettle of steaming water may be

brought into the room. This use of steam is even more important when a severe catarrhal laryngitis or bronchitis is present. Under such circumstances aromatic and sedative medicaments, such as the compound tincture of benzoin may be volatilized by being placed upon the surface of the steaming water.

The habit, fortunately obsolete for the most part now, of bundling up measles patients with an excess of bed-clothes is to be deprecated.

Mothers should be instructed that the guide in this matter is the comfort of the patient. In changing the bed linen of patients in the winter months it is advisable to warm the sheets before they come in contact with the patient.

It will be found necessary to protect the eyes of measles patients against too strong rays of light. It should be remembered, however, that it is not necessary to make a room absolutely dark in order to accomplish this purpose. Just sufficient light should be excluded to make the patient comfortable. The complete shutting out of daylight is not only depressing, but the air is robbed of the purifying and germ-destroying influence of the sun's rays.

Patients with measles may be sponged daily with tepid water.

In order to avoid complications which arise from the catarrhal inflammation of the nose, mouth and conjunctiva, it is well to employ the following *preventive measures* as a routine. The mouth should be washed several times a day with a solution of boric acid to which a little glycerin and a few drops of oil of wintergreen may be added, or instead some other mild antiseptic wash may be employed. By this precautionary measure the liability to ulcerative stomatitis, a by no means rare occurrence, is lessened.

The nares should be irrigated every few hours with a decinormal saline solution. Care should be taken that the syringe is gently manipulated and the forcible projection of fluid into the nose avoided.

Comby prefers spraying of the nose, mouth and throat with a steam atomizer. He states that Siredey obtained excellent results by this method at l'Hôpital d'Aubervilliers; before this treatment was used 50 cases of measles gave 23 complications (46 per cent); since the employment of the spray 53 cases have only furnished 7 complications (13 per cent). The genitalia, particularly in girls, should be kept scrupulously clean owing to the vulnerability of these parts to gangrene involvement. In addition to the use of soap and water a weak solution of bichloride of mercury or a saturated solution of boric acid may be employed.

Measles patients should always be *confined to bed* for the entire febrile period of the disease; in severe cases the patient should not be allowed to leave bed until a week or ten days after the termination of fever. During the cold and rainy seasons this precaution should be carefully observed. During the balmy days of late spring or summer one need not adhere so rigidly to this rule. Season and climate will influence the duration of the sojourn in-doors. Ordinarily the patient should

not go out for ten days to two weeks after the subsidence of fever; this period should be increased in cold, wintry weather and abbreviated during a warm and dry spell.

Diet.—For children, milk, preferably diluted with barley-water, is the best diet. This not only constitutes the most assimilable and nourishing food, but helps to assuage the thirst and acts on the kidneys. When the temperature is high the milk may be taken cool and will be found to be most acceptable to the patient. Where it is distasteful to a child it may often be rendered more palatable by flavoring it with a little extract of vanilla. As measles is a disease of short duration it is not essential to force nourishment upon the patients as in more protracted affections, such as typhoid fever.

It will be found that when the temperature is high children will want nothing but cool milk; later there will be a desire for a more varied dietary. As the fever declines there is no objection to the use of junket, farina, milk toast, broths, arrow root, rice, custard, strained oatmeal, soft-boiled eggs. It will be well to avoid those cereals which, by reason of their husk, are apt to excite diarrhea.

For the relief of thirst, apart from the use of cool milk, the patient may partake freely of water, provided it is not iced. In older children carbonated water is often gratefully received, or water acidulated with lemon or orange juice.

There is no objection to the use of ice-cream, provided it is taken in moderation.

Medical Treatment in the Complicated Cases.—Mild cases of measles require but little medication; the nursing is of greater importance. It may be necessary to relieve constipation in the beginning. No irritant purgatives should be employed, but rather such gentle remedies as castor oil or syrup of rhubarb, or a simple enema may be given. Drastic drugs might lead to a catarrhal inflammation of the intestines, to which measles patients are already predisposed. More often the physician will be called upon to check excessive bowel movements. If these are allowed to continue they soon exhaust the vitality of the patient. Usually the diarrhea can be controlled by a mixture containing paregoric and bismuth; if this does not suffice the deodorized tincture of opium may be used instead of paregoric.

Where the bronchial catarrh is slight no treatment is necessary. When there is much cough it will be necessary to allay it by one of the simple cough mixtures. The well-known "brown mixture" may be administered or a combination containing a little bromide of soda and ipecacuanha may be used. For severe and incessant cough one may be obliged to resort to opium; it must be remembered that this drug must be used with caution in young children. Five to 20 drops of paregoric, according to the age of the child, may be given every few hours.

The fever, when of moderate grade (102° F.), will require no treatment. It is customary to prescribe some simple febrifuge containing

a little tincture of aconite, potassium citrate and spirits of nitrous ether; this preparation has a gentle diuretic and diaphoretic action. When the temperature reaches 104° or 105° F., and particularly when it is accompanied by marked nervous symptoms, such as restlessness, delirium, stupor or convulsions, more active antipyretic treatment is demanded. Of all measures for the reduction of temperature, hydrotherapy is to be preferred. Cold tub baths are usually not well borne by young children, and it is best to employ tepid or warm baths, except where the fever cannot be thus controlled. Immersion in a bath of 85° to 90° F. will frequently bring down the temperature and quiet the disturbed nervous system. These baths may be repeated as often as the occasion demands. In those cases in which the temperature is not sufficiently controlled by this means recourse may be had to the use of cold sponge baths or the use of the wet pack. The ice-cap may be used as an adjunct to any of these measures.

When the temperature is high and the extremities cold the patient may be immersed in a hot bath with or without the addition of mustard; in such cases the ice-bag should be applied to the head. The cold bath under such circumstances is badly borne, as the depression is too great for an already weak heart.

The hot bath with mustard is also useful in those cases in which the eruption is imperfectly developed or unusually slow in making its appearance.

The reduction in the body temperature is accompanied by an amelioration of the pronounced nervous symptoms which accompany hyperpyrexia. Where for any reason hydrotherapy cannot be employed, one may resort to the use of some of the coal-tar antipyretics. Antipyrin usually acts very well in children. It has been extensively employed by many physicians with satisfactory results. Not only is there a reduction in the temperature, but violent nervous manifestations, when present, are promptly quieted; 1 to 3 gr. repeated according to indications will usually suffice. Comby has used this drug extensively in measles, giving it in dosage of 7½ to 15 gr. We would feel a hesitancy about administering such a dose to a child, yet Comby states that he has never seen any bad results therefrom; a reduction of temperature of 1° or 2° F. was obtained, which lasted from two to four hours. Phenacetin may, if desired, be employed, instead of antipyrin. While these drugs usually act well, hydrotherapy is ordinarily to be preferred.

Treatment of Complications.—Measles as an uncomplicated disease nearly always ends in recovery; it is its complications which render it frequently a grave and fatal affection. The preventive measures to be pursued have already been discussed. The complicating disorders must be treated much in the same manner as when they occur independently of measles.

Nervous Symptoms.—The ushering in of an attack of measles with convulsions is not of bad augury unless they persist; convulsions in

children take the place of the chill in adults. Where the seizure is brief no special treatment is necessary; when it is prolonged or repeated there is a possibility of a cerebral hemorrhage resulting therefrom and measures should be taken to check the convulsions. A few inhalations of chloroform will frequently control the paroxysm, after which chloral hydrate or antipyrin should be administered. An ice-bag to the head will also be found to be of assistance.

Restlessness, stupor or delirium can be controlled by the hydrotherapeutic measures mentioned, for they almost always occur in association with high temperature.

Skin.—The skin should be kept scrupulously clean throughout the attack; this may be accomplished by sponge baths with alcohol and water or mild antiseptic solutions.

Itching of the skin may be so intense as to necessitate measures for relief. A lotion containing 1 dram each of carbolic acid and glycerin to the pint of water or an ointment of 10 gr. each of carbolic acid and camphor to the ounce of vaseline will control the pruritus. Not infrequently impetigo vesicles and pustules develop about the nose, mouth or ears as a result of pyogenic infection of the skin from purulent discharges. An ammoniated mercury ointment, 10 gr. to the ounce, will effect the disappearance of these lesions.

Ulcerative Stomatitis.—Ulcerative stomatitis is to be treated by the frequent use of antiseptic mouth washes, such as diluted Dobell's solution or hydrogen peroxide. Where there is much ulcerative action benefit will be derived from painting the ulcers each day with tincture of iodine.

Cancrum Oris.—When that frightful complication *cancrum oris* develops prompt and energetic treatment is demanded. As soon as the condition is discovered the patient should be given a few whiffs of an anesthetic, the pultaceous mass upon the mucous surface of the cheek curetted away and the base thoroughly cauterized with fuming nitric acid. If despite this the gangrene should appear upon the cutaneous surface of the cheek, the affected area should be promptly and freely excised. One must not be deterred for fear of the resulting disfigurement, for only the most radical treatment will give a chance for life. The vital powers should be supported by concentrated liquid nourishment and by stimulants.

Coryza.—When coryza is an annoying symptom considerable relief will be afforded by irrigating with saline solution and subsequently spraying the nares with albolene containing 2 gr. of menthol to the ounce. This procedure may be repeated every few hours if necessary.

Nose-bleed.—Nose-bleed, when moderate, need not be interfered with, as it lessens the congestion of the nasal structures. When it is severe or persistent it may be checked by the injection of hot water, a solution of antipyrin, or, if necessary, the perchloride of iron. When the hemorrhage is from the anterior portion of the nose the nares may be plugged with sublimated absorbent cotton.

Conjunctivitis.—The conjunctivitis is often sufficiently pronounced to require measures for its relief. The light in the sick-room should be kept subdued. Cool, moist compresses may be applied to the lids, and a boric acid eye-wash instilled several times a day. Where there is considerable gluing together of the lids by the drying of the conjunctival discharge, the borders of the lids should be anointed with an ointment of ½ gr. of the yellow oxide of mercury to the dram of vaseline.

Laryngitis.—Laryngitis is present in the vast majority of cases. When it is mild the application of moist compresses to the neck will be all that is necessary. These may be applied cold and changed three or four times in the course of twenty-four hours. When the laryngitis is accompanied by spasmodic paroxysms the compresses should be hot. The atmosphere of the room should be kept moist. When symptoms of croup are pronounced it is a good plan to make a tent of the bed-clothing and direct the spout of a croup kettle into the tent. Lime-water may be evaporated instead of ordinary water; the patient should also be encouraged to drink freely of water, particularly alkaline waters. Jacobi recommends the internal administration of the iodide of potassium in moderate doses and also an opiate at night. Dover's powder has long been regarded as a useful remedy in relieving laryngeal spasm.

In laryngeal stenosis von Jürgensen advises a hypodermic injection of apomorphine hydrochlorate sufficient to induce vomiting. It should be remembered that a persistent stenosis of the larynx after measles means the presence of a false membrane, and that this may result either from the presence of the streptococcus or the diphtheria bacillus. This serious condition requires prompt and energetic treatment. If *diphtheria* is suspected the usual treatment, including the administration of antitoxin, should be immediately instituted. The prognosis appears to be equally grave whatever be the character of the membranous exudate, for bronchopneumonia is extremely apt to supervene. When the stenosis leads to urgent dyspnea intubation becomes necessary. This operation will give temporarily relief, but it seldom averts the fatal outcome.

Bronchopneumonia.—Bronchopneumonia is the most frequent and the most fatal of all of the complications of measles. Every effort should be made to prevent the development of this dreaded complication by attention to hygiene and nursing, as already pointed out. The utmost vigilance is necessary to detect the earliest symptoms of this disease. Holt aptly says: "Very little can be done for the disease, but much can be done for the patient." The chest should be enveloped in a jacket of cotton-batting or oiled silk. Counterirritation in the form of mustard-wheat-flour paste may be applied to the chest from time to time. When the temperature is high and the pulse of good volume ice poultices over the chest accomplish a double purpose.

Children should not be allowed to be continuously in the same position, but should be moved from time to time. Infants may be carried in the nurse's arms. Steam inhalations will be found useful when there is much bronchial secretion; these may be medicated with a little creosote. No antipyretic treatment is necessary unless the temperature rises above 103° F. The coal-tar derivatives should, in general, be avoided, as they are depressant in sufficient dosage. Hydrotherapy should be depended upon to lower the temperature when it is excessive and to allay the accompanying nervous symptoms. For this purpose the graduated bath, the wet pack, sponge bath, or ice-cap can be employed. Friction of the extremities during the bath will help to maintain the peripheral circulation. Brandy may be administered before the bath and heat applied to the feet afterward.

Where there is much cyanosis a warm mustard bath with the ice-cap to the head will be found useful.

The alternate application of hot and cold douches favors deep respiration, a condition eminently to be desired. Jacobi says: "Warm bathing and cold affusion in a warm bath will be of good service, for it is necessary that the patients, particularly small children, should cry. Unless they cry they will suffocate." For the purpose of stimulating deep breathing and expectoration Thomas recommends the use of a folded sheet wrung out of cold water wrapped around the chest; this procedure may be frequently repeated, particularly if the temperature is high.

Emetics and depressant expectorants are to be avoided.

Whiskey and brandy are of great value, but should be reserved until they are needed; they should not be pushed in the beginning, before the heart shows evidence of weakness. When the pulse becomes small and rapid they are to be administered freely; a child one year of age will bear 1 or 2 ounces of whiskey a day. Strychnine is a valuable remedy and may be given in doses of $\frac{1}{300}$ gr. every three or four hours to a child one year of age.

Nitroglycerin or the nitrite of amyl or injections of camphor in oil are useful to tide over acute cardiac depression.

When cyanosis makes its appearance oxygen should be resorted to. It may be given for long periods freely mixed with air. A good plan is to introduce the oxygen beneath a bed-tent. Sudden collapse should be combated by the use of oxygen, whiskey, strychnine and a hot mustard bath.

Isolation.—In treating cases of bronchopneumonia following measles in hospitals it is a wise precaution to isolate these patients from the uncomplicated measles patients. Holt says: "Twice in one institution have I seen regular epidemics of bronchopneumonia occur with outbreaks of measles, in some of the wards nearly every case of measles developing pneumonia."

In the Hôpital des Enfants Malades, at Paris, all cases of bronchopneumonia are treated in isolated compartments in the ward. The

partitions are 8 feet high and constructed in part of glass; each compartment is open at the top and has a window opening upon the exterior. It was deemed desirable to isolate cases of bronchopneumonia because the disease was considered very infectious and because the severity of the attack appeared to be diminished thereby.[1]

Otitis Media.—Otitis media is a common complication of measles. If neglected it may give rise to more serious conditions, such as mastoid or cerebral abscess.

By the assiduous use of mild antiseptic solutions in the nose and throat in measles much may be done to prevent extension of inflammation to the middle ear.

The Eustachian tube of very young children is relatively of large size, and pyogénic germs in the naso-pharynx can find ready access to the middle ear. The keynote of prophylaxis, therefore, is cleanliness. The naso-pharynx should be sprayed with warm, bland liquids, such as boric acid or decinormal saline solution, after which a weak mentholated liquid vaseline should be introduced. Children should be encouraged to blow the nose frequently to dislodge the adherent mucus. In very young children, and especially when adenoid vegetations are present, Downie[2] advises gentle inflation of the nostrils by means of the Pollitzer bag. This manipulation should not be entrusted to a nurse, but should be performed by the physician himself. The child is instructed to forcibly breathe out through the mouth at the moment the air is inflated through the nose. In this manner the muco-purulent discharge is forced into the mouth from the naso-pharynx.

When otitis develops and the pain is severe measures must be employed for its relief. Heat should be applied to the external ear; dry heat is to be preferred to moist applications. A hot salt, bran or water bag may be placed over the ear, with a towel interposed. A few drops of a 3 per cent solution of cocaine instilled into the ear often gives relief; oily solutions for this purpose are to be avoided. Tincture of iodine may be painted over the mastoid region. It will be necessary in some cases to give an opiate, preferably in the form of paregoric, to relieve the pain and induce sleep.

The persistence of the pain with an increase in temperature indicates the performance of a paracentesis tympani.

Incision should be made in the posterior-inferior segment. Relief is often immediate, although pus may not be discharged until later. It is a good plan to expel the pus after puncture by inflation of the nose with the Pollitzer bag. The auditory meatus should then be cleansed with a warm saturated solution of boric acid or a 1 to 5000 solution of corrosive sublimate. The patient should be encouraged to lie upon the affected side to favor evacuation. The use of absorbent cotton in the ear should be avoided.

[1] Quoted by Dawson Williams, loc. cit.
[2] Quoted by Williams.

Urine.—The urine should be examined from time to time to exclude the presence of kidney involvement. Nephritis is relatively rare in measles, but it has been discovered often enough to justify some care in this direction.

During *convalescence* children should be restrained from the excessive use of the eyes, which are still in a weak condition. The persistence of cough, particularly with slight evening rises of temperature, should put one on guard against the possible development of tuberculosis. Children thus affected should, if possible, be taken to a locality where the climate is warm, dry and equable. Creosote and cod-liver oil will be found to be among the most useful remedies for this persistent cough.

CHAPTER X.

RUBELLA.

Definition.—Rubella is an acute, contagious, epidemic disease, characterized by an eruption of barely elevated, rose-colored macules, slight catarrhal symptoms, and mild febrile disturbance, running a course lasting usually three or four days. Rubella is a specific entity, unrelated to either measles or scarlet fever, and protecting only against future attacks of the same affection.

Synonyms.—*German measles; Rötheln.* There is an embarrassment of riches in the various designations applied to this disease. The Germans use the terms *rötheln* and *rubeola;* the French call it *rubeole.* The latter term being used at times to denote true measles, it is confusing to apply it to another disease. Among other appellations are *rubeola sine catarrho* or *incocta, rubeola notha, rubeola epidemica, rubeola morbillosa, rubeola scarlatinosa, rosania, roseola, roseola epidemica, rosalia, exantheme fugace, essera Vogelii; hybrid, bastard, spurious* or *imperfect measles; hybrid* or *bastard scarlatina, rougeole fausse, feuer masern, German measles, French measles,* etc. The last-named terms should not be employed, for rubella is a disease entirely distinct from measles, although often strongly resembling it. Griffith counsels the adoption of the Latin term *rubella,* which was introduced by Veale in 1866 and accepted by Squire and others.

History.—The vagueness of the very early medical writings and the use of confusing names make it difficult to establish the origin of the exanthematous diseases with any degree of accuracy.

The first accurate and undoubted references to the disease were published in the middle of the eighteenth century by the German physicians de Bergen (1752) and Orlow (1758). But some of the writers in the next half century evidently confused the disease with scarlatina and other affections, for neither the descriptions nor the mortality-rate conform with that of rubella.

Homans, of Boston, in 1843, was the first physician in this country to call attention to the disease. Cotting published papers on the subject in 1853 and 1871. Howard, in 1871, and J. Lewis Smith, in 1874, also directed the attention of American physicians to the existence of rubella. The chief epidemics reported in this country have been by Hatfield (110 cases), Park (over 100 cases), Earle (120 cases), Edwards (166 cases), Kingsley (21 cases), Atkinson, Griffith and Hardaway.

At the present day there is a unanimity of opinion concerning the existence of rubella as a disease *sui generis.*

THE ETIOLOGY OF RUBELLA.

It is generally recognized that rubella, like the other exanthematous diseases, is derived from and begets a like disorder. It confers protection only against rubella, and no immunity against it is granted by an attack of measles or scarlet fever.

Many of the earlier writers doubted and even denied the contagiousness of rubella, but there is at the present day a unanimity of opinion concerning its transmissibility. As to the *degree of contagiousness* views are somewhat divergent. Chadbourne and J. Lewis Smith regarded it as feebly contagious; Thomas, Liveing, Tongue-Smith, Bourneville and other, as less contagious than measles; Jacobi, Dukes, Squire and Griffith look upon it as very contagious, and Edwards[1] believes that "rubella is one of the most contagious of all of the eruptive fevers." Griffith states that in an institution of 100 children 37 took the disease despite prompt and careful isolation. In another institution 26 per cent were attacked. Klaatsch believes that the degree of contagiousness varies in different epidemics.

Hatfield[2] reports an asylum epidemic in which 110 inmates out of 196 contracted the disease.

From our experience at the Municipal Hospital we are inclined to believe that a larger number of children escape rubella when this infection is introduced into the wards than escape measles under similar circumstances.

Rubella is essentially an *epidemic* disease and appears to be more prevalent in the winter and spring seasons. The disease is about as common as measles, with which affection it has doubtless often been confounded. The infection of rubella seems to be more tenacious and persistent than that of measles. It is, therefore, more apt to be carried by *fomites* in the garments of third persons than is measles. Edwards alleges that about 75 per cent of his cases could be directly traced to infection from bunks of ships, and states that Emminghaus, Thomas, Veale and others considered such an origin proved. Corlett[3] remarks that rubella corresponds more with scarlet fever than with measles in the persistence of the vitality of the contagium.

Opinions are at some variance in regard to the period of greatest contagiousness. Thierfelder looked upon the stage of convalescence as the time at which the disease ws most transmissible. Squire considered all stages contagious, from the preëruptive period late into convalescence. Edwards coincides with this opinion. Griffith concludes, from his observation in institution epidemics, that rubella is certainly contagious at a very early date, for prompt isolation failed to check the extension of the disease.

Age. – Rubella behaves much like measles as regards age incidence. Infants under six months of age usually escape the infection, although now and then the disease will be contracted. We have seen an infant

[1] Rubella, Keating's Cyclopedia of Diseases of Children, Philadelphia, 1889, p. 687.
[2] Chicago Med. Exam., August, 1881.
[3] Loc. cit.

six months of age live and remain well for months in a ward in which cases of rubella were constantly appearing. Smith, Roth, Steiner and Hardaway have recorded attacks in early infancy, and Scholl reports a case occurring in a child a few days after birth, the mother having suffered from the disease two months previously. As in measles, those who escape the disease in childhood may contract it in adult life; indeed, even in advanced years, as is attested by Seitz, who reports a case in a woman seventy-three years of age.

Emminghaus saw only 2 adult attacks among 42 cases. Thomas noted 3 among 77 cases; Kassowitz observed 5 in 64 cases and Thomas but 1 in 100 cases. Edwards does not believe that adult life confers any special immunity; he regards infrequent exposures to the disease, and protection by an attack in childhood as the cause of the comparative rarity among adults.

Thomas holds a rather different view. He says: "After the fortieth year the susceptibility is nearly lost, and we may consider it as essentially weakened at puberty and as steadily diminishing subsequently." In Forchheimer's[1] experience more physicians have been attacked by rubella than by all the other exanthematous diseases taken together. He adds that "With the exception of variola, possibly no disease of this class so frequently affects adults."

THE SYMPTOMATOLOGY OF RUBELLA.

Period of Incubation.—Different observers have assigned incubative periods to rubella varying from five days to three weeks. This variable duration is regarded by Griffith as one of the diagnostic features of the disease and in striking contrast with the fixed incubation period of measles. To indicate the divergent observations of different clinicians we present a table compiled by Forchheimer, to which we have made additions:

PERIODS OF INCUBATION OF RUBELLA.

Atkinson	14 to 21 days	Hardaway	2 weeks or longer
Balfour	2 weeks	Hatfield	10 days
Boudet	12 to 14 days	Jacobi	14 to 21 days
Bourneville	8 days	Kassowitz	2 to 3 weeks
Bricon	8 to 10 days	Klaatsch	2½ to 3 weeks
Bristowe	1 week	Longstet	18 days
Cheadle	15 days	Mettenehimer	2 weeks or longer
Clausen	17 to 20 days	Musser	Just 6 days in 1 case
Cotting	3 weeks	Picot	2 to 3 weeks
Cullingworth	2 weeks	Pollock	6 to 16 days
Cuomo	17 days; never less	Juhel-Renoy	15 days
Duckworth	16 days	Robinson	6 to 7 days
Duke	15 to 16 days	Scholl	5 to 21 days
Earle	17 to 21 days	Steiner	10 to 14 days
Edwards	10 to 12 days	J. L. Smith	7 to 21 days
Eichhorst	2 to 3 weeks	Tongue-Smith	14 days
Emminghaus	2 to 3 weeks	Squire	8 to 21 days
Gerhardt	2 to 3 weeks	Thierfelder	2 weeks or longer
Glaister	4 to 5 days or longer	Thomas	2½ to 3 weeks
Goodhart	2 weeks or longer	Vacher	13 days
Griffith	5 to 11 days		

[1] Rubella, Twentieth Century Practice of Medicine, p. 180.

It is thus seen that the incubation may be either shorter or longer than that of measles. Eleven writers have noted minimum periods of five to eight days, and no less than 32 have seen the period extend beyond fourteen days.

During the stage of incubation the patient is entirely free of any disturbance of health except, perhaps, in extremely exceptional cases.

Period of Invasion.—In most cases of rubella this stage is either devoid of symptoms or presents only mild manifestations which are readily overlooked. It would appear that the more severe the attack is to be, the more apt is it to be preceded by pronounced prodromal symptoms. In the vast majority of our cases at the hospital the eruption was the first sign to attract attention. In a severe attack in a trained nurse, the symptoms of which will be fully detailed later, there was, however, a distinct and protracted stage of invasion. This nurse was on night duty in a ward in which rubella existed. She was taken ill with headache and sudden vomiting; the emesis was persistent, the patient vomiting four or five times each day and retaining nothing. There were also feverishness, continued headache, recurring chilliness, perspiration during sleep, restlessness and weakness. *Four and a half days later* the eruption appeared. No catarrhal symptoms whatever were present. This case must be regarded as presenting exceptional initial manifestations.

While most writers refer to very mild and brief prodromes, some rather severe invasive symptoms have been described. Edwards[1] noted in a severe epidemic in the Philadelphia Hospital the following symptoms: chilliness, languor, faintness, headache (more or less severe), pain in the back and limbs, coryza, red and watery eyes, sore throat, cough, occasionally a hoarse, husky voice and a temperature from 100° to 103° F.; nausea and vomiting, delirium and convulsions and epistaxis were observed in 3 cases.

Other unusual prodromal symptoms have been recorded. Prioleau reports 2 cases of hemorrhage from the eyes and ears; vomiting is mentioned as a rare symptom by Smith, Murchison, McLeod and Emminghaus; convulsions, by Smith, Lindwurm, Cuomo and Alexander; delirium by Hardaway and Cuomo. Nymann observed rigor in 19 out of 119 cases; Earle, Kingsley, Thierfelder and Griffith mention a slight redness preceding the eruption, and Cuomo (in 7 cases) and Edwards (in 4 cases) a prodromal erythema.

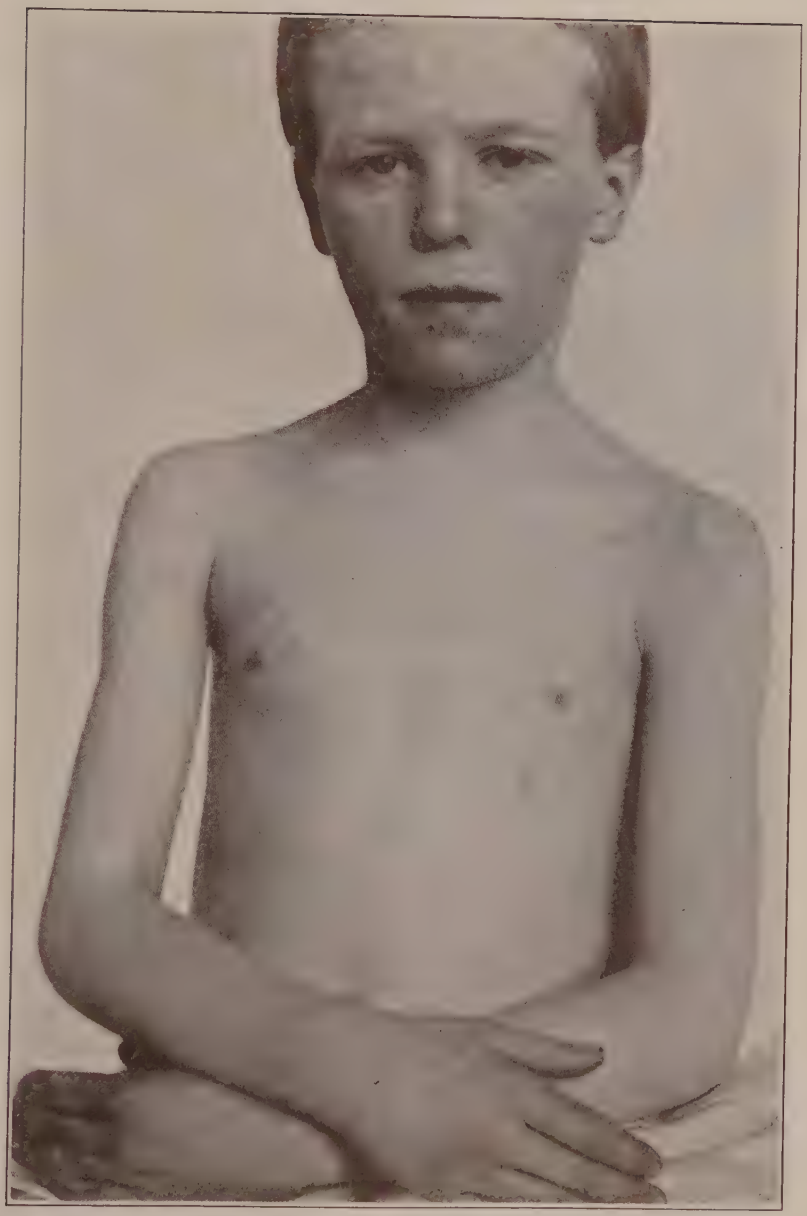
Such symptoms as those detailed are exceptional, but nevertheless of interest. The experience of most observers is that the prodromal symptoms are absent or mild, consisting of drowsiness, anorexia, "liquidy" eyes, sneezing, slight cough, etc.

Earle found that prodromal symptoms were more frequently present in adults than in children.

As to the duration of the invasive period, opinions differ somewhat;

[1] Loc. cit.

PLATE XXI



Eruption of Rubella, Showing Discrete but Closely Set Macules.

we would subscribe to the statement of Thomas, endorsed by Hardaway and Griffith, that in the vast majority of cases the prodromal stage is at most no longer than half a day. At the same time we recognize that it may vary from a couple of hours to five days. Various writers assign periods intermediate between these two extremes. It would seem that long periods of invasion pressage attacks of greater severity than brief periods.

Period of Eruption.—A half-day or so after the onset of mild invasive symptoms, or in many cases without any prodroma at all, the eruption of rubella makes its appearance. The rash is commonly the first symptom to attract attention, the other milder initiatory disturbances then being recalled. Not infrequently a child awakens in the morning with the eruption visible upon the face. In our cases at the Philadelphia Hospital for Contagious Diseases, all of which developed in scarlet fever convalescents, the rash was frequently discovered when the children were lined up for inspection during our visits.

Most writers coincide in the view that the eruption appears first on the face; other locations are, however, mentioned by some observers as the initial site. Liveing and Morris state that it appears first on the trunk; Murchison, Day and Balfour speak of the breast and arms as first attacked; Willcocks and Carpenter, the face and margin of the hair; Thomas and Corlett, the face and scalp. Patterson and Copland assert that it comes out simultaneously on different parts of the body.

In noting the eruption a short time after its appearance upon the face we have seldom failed to find it to some extent on the trunk and arms.

In a severe case in a trained nurse (to which reference has already been made) the eruption was carefully looked for by another nurse occupying the same room and was observed to first appear at 3 A.M. on the *legs below the knees;* it then spread upward and by 6 A.M. was noticed on the wrists. At 3 P.M., the hour of our examination, it was present on the legs, arms and trunk. The face was flushed, but no distinct eruption was seen in this region until the following day.

It is evident that while the eruption of rubella normally appears first on the face, thence extending downward, anomalous cases may occur in which the origin is in other regions.

The exanthem spreads quite rapidly over the body in the course of twenty-four to forty-eight hours. It is interesting to note, however, that the maximum intensity of the rash is not simultaneously noted on the entire cutaneous surface. It is not unusual for the face, chest and arms to show the eruption at its height while the legs are yet unaffected. When the lower extremities exhibit the exanthem in its greatest intensity it is fading upon the face and upper part of the body. In other words, the rash often seems to pass over the cutaneous surface in a sort of *wave-like progression.* The duration of the eruption at its height in any given region is from a few hours to half a day.

The more severe the attack, the longer is the period of maximum intensity and the longer the duration of the eruption.

This peculiar progression of the eruption is commented upon by Thomas in the following words: "It happens with tolerable frequency that the maxima of its development occur at varying times upon different portions of the body." Some writers, particularly Emminghaus, Roth, Mettenheimer and Hardaway, attach to this eruptive sequence great importance, regarding it as one of the safest diagnostic signs of rubella. Griffith agrees with Thomas' statement as to the tolerable frequency of this occurrence, but questions its diagnostic value, as he has nearly as often observed that the rash persisted with equal intensity on the face while it spread to the rest of the body, reaching its acme everywhere upon the second day.

Character of the Eruption.—The eruption, in its most typical form, consists of pin-head to lentil-seed-sized, pale rose-tinted, slightly elevated, moderately defined macules. The lesions are usually rounded or oval, but may be irregular. The elevation is scarcely sufficient to warrant the use of the term papules, but is appreciable to the finger passed over the surface of the skin. The macules are ordinarily discrete, with considerable intervening pale skin, particularly at the onset of the eruption and on the trunk. Later they are apt to become more closely set and may coalesce, with the production of irregular patches resembling measles or sheets of eruption of a scarlatiniform character.

Ordinarily, macular grouping, such as is seen in measles, is absent, but we have now and then seen distinct linear and crescentic configuration indistinguishable from that observed in measles. Rubella in its purest form, however, shows smaller, more regular and more discrete lesions than those of measles, which are inclined to present an irregular blotchy appearance. The *color* of the macules of rubella has been described as a pale rose-tint or rosy-red by most writers. Shuttleworth refers to it as a brownish-red. The color doubtless varies to some extent in different individuals, as does the tint in all eruptive diseases, but it may be said in general that it is ordinarily not as vivid as the eruption of scarlet fever, nor as dusky or bluish as the measles exanthem.

The discreteness of the slightly elevated macules gives the eruption its distinctive appearance, the reddish spots standing out in striking contrast with the pale integument. Confluence is, however, frequently noted in certain areas, particularly on the face. On the second or third day of the eruption it is not uncommon for the rash to become paler in tint and to assume a more diffuse appearance.

Pressure or irritation of the skin seems to increase the intensity of the eruption and to encourage confluence. Klaatsch and Griffith both report cases in which the eruption was particularly well developed in circular bands above the knees, where the garters had made pressure. In scarlet fever, on the other hand, pressure, such as is produced by garters, is apt to produce anemic or pale bands in the areas thus affected.

PLATE XXII

Rubella Exhibiting a Fine Macular Eruption on the Second Day.

Distribution of the Eruption.—The face almost invariably exhibits an abundance of eruption, especially upon the forehead, cheeks and chin. The lesions may be so copious as to produce the appearance of slight edema. The eruption does not respect the circumoral region as does the exanthem of scarlet fever. The scalp is profusely covered, as is also the neck. The chest, abdomen, back and arms show rather less eruption; the buttocks and posterior aspect of the thighs, owing, perhaps, to pressure, commonly exhibit eruption in such profusion as to present confluent patches. The legs, as a rule, are the seat of the least eruption, the lesions often being widely scattered. It has been

FIG. 121.—Rubella, similar eruption present on body.

asserted by some writers that the palmar and plantar surfaces are exempted, but this is not true, as lesions are not infrequently found in these regions in well-pronounced attacks. The above outline presents the distribution of the eruption in normal cases; it is not rare for departures from this to take place.

Barthez and Rilliet have noted the fading of the eruption followed by the reappearance of the same upon the same day or later. Griffith also mentions a case in which it was invisible during one day and returned.

Duration of the Rash.—The duration of the rash is influenced by the intensity of the eruption and the character of the epidemic. The various periods assigned by different writers are here tabulated:

Aitken	4 to 5 days (bad cases 6 to 10	Gerhardt	½ to 1 day
Alexander	14 days (1 case)	Griffith	2 to 3 days
Alibert	2 to 3 days	Hatfield	4 days
Balfour	4 to 6 days	Kingsley	2 to 4 days
Barthez	2 to 3 days	Klaatsch	1 to 5 days
Bourneville	2 to 3 days	Liveing	5 to 7 days
Bricon	2 to 3 days	Maton	3 to 4 days
Carpenter	1 to 4 days	Nymann	2 to 4 days
Claussen	3 days	Picot	3 to 4 days
Copland	4 to 5 days	Rilliet	2 to 3 days
Corlett	2 to 4 days	J. G. Smith	3 days
Edwards	2 to 15 days; average 5	Thomas	2 to 3 days
Emminghaus	2 to 4 days	Trousseau	1 to 2 days
Forchheimer	Not exceeding 5 days	Willcocks	1 to 4 days

It will be seen from the above figures that the duration of the eruption offers considerable latitude. The long periods are doubtless isolated instances. In about 100 cases which we have had the opportunity of observing, the rash did not persist beyond three days, save in the case of the nurse in whom it lasted five days. In a

Fig. 122.—Rubella exhibiting an eruption quite indistinguishable from measles.

great many of the children the eruption was scarcely apparent after the first twenty-four hours; the average duration was certainly not more than two days. The brief duration is, perhaps, to be accounted for by the very mild type of the epidemic. The average duration in over 200 of Edwards' cases was five days; the type of the epidemic which he observed was, however, distinctly more severe than ours.

PLATE XXIII

Rubella in a Man, Aged Twenty-one Years, with the Scarlatinoid Type of the Exanthem.

The rash appears to persist longer in some regions than in others, possibly the regions of greatest intensity. Edwards says that the face and upper chest exhibit the most persistent eruption; our experience coincides more with that of Griffith, who regards the face and buttocks as the seats of the most protracted eruption.

Anomalous Features of the Eruption.—In rare instances miliary vesicles have been noted upon the reddish macules. This has been observed by Curtman, Cuomo, Thomas, Hardaway and Copland.[1]

Petechial spots have been recorded by Dunlop and likewise by Cheadle; Erskine reports similar lesions on the uvula and soft palate. A purpuric rash was also observed by Glaister.

Claussen makes mention of lesions which gave the impression of small shot being buried in the skin. Griffith saw an unusual eruption which also imparted a shotty feel to the finger.

Scarlatiniform Variety of Rubella.—Thus far reference has only been made to normal rubella and to the form which bears more or less of a resemblance to measles. There are other cases in which the exanthem bears a strong resemblance to that of scarlet fever. Some writers of prominence make no mention of this variety and express astonishment at any suggestion of similarity between the rashes of rubella and scarlatina. Thomas says: "According to my observations the exanthem of rubeola (rubella) possesses a similarity to that of measles only, not the slightest to that of a normal scarlet fever." Bristowe and Bourneville and Bricon entertain similar views. These opinions may be attributed to the fact that the scarlatiniform variety of rubella has not come within the range of the personal experience of these physicians.

Mention could be made of a large number of writers who have observed this variety. Hatfield speaks of an epidemic in which the rash in many cases was indistinguishable from measles, and in other cases strongly resembled scarlet fever. J. L. Smith refers to a case which, had he been guided alone by the eruption, he would have regarded as a mild scarlet fever. Griffith describes a case in which the eruption was at first macular, yet on the second day it so closely resembled scarlet fever that he was unable for several days to make a diagnosis. The whole body was covered by a general scarlatinal blush and nowhere could a single macule or papule be found. A short time afterward the brother took rubella.

We have seen in the Philadelphia Hospital for Contagious Diseases 1 or 2 cases of rubella with scarlatiniform eruptions in children convalescent from scarlet fever.

Griffith,[2] from a careful study of a large number of cases, comes to the conclusion that there are two easily recognized types of variation form the character of the eruption in a normal case:

"1. An eruption in which the spots are for the most part nearly or

[1] Mentioned by Griffith: Loc. cit.
[2] Loc. cit. p. 15.

fully the size of a split pea, more or less grouped, and, in fact, having the greatest resemblance to measles.

"2. A rash which is confluent in patches or universally not elevated, and which produces a uniform redness closely simulating that of scarlatina. Very careful examination will often reveal a few papules amid the general diffuse redness."

Desquamation.—Upon the subsidence of the eruption a delicate brownish or yellowish staining may be noticed for a short time.

A slight branny or furfuraceous desquamation occasionally follows the disappearance of the rash. The development of this scaling is proportionate to the severity of the attack and the intensity of the eruption. Many writers, including Steiner, Thomas, Fleischmann, Brodie, McLeod, Wilson, Goodhart, Cuomo, Bourneville and Bricon have not observed desquamation. Edwards, on the other hand, in a severe epidemic, discovered desquamation in all of his cases. In quite a number the scaling was well marked; in others it was limited to certain regions, especially the nose. The buccal cavity, particularly the throat proper, participated in the desquamative process. The peeling was usually furfuraceous, beginning in the center of the eruptive patch and extending to the circumference. Larger scales were seen on the hands and feet. The average duration of desquamation was three days, but Edwards has seen it last twenty days. In our cases, which it will be remembered were very mild, it was rare to see any desquamation.

Associated Symptoms of the Eruptive Stage.—**Fever.**—The extent of febrile reaction in rubella is largely dependent upon the severity of the individual attack and the character of the prevailing epidemic. The variant observations of different writers on this point is evidence of the truth of the above assertion. There are some epidemics in which there is but an insignificant rise of temperature, if, indeed, there be any fever at all. Nymann failed to observe any appreciable rise of temperature in 58 out of 119 cases. Emminghaus, Thomas, Vogel, Wunderlich, Earle, Picot and others have all seen afebrile cases.

On the other hand, in severe cases high fever may be present. Edwards saw cases with temperature of 103° and 104° F. McLeod's cases ranged from 100° to 105° F. Cheadle reports an epidemic in which the initial temperature was 103° F., later reaching 104° and 105° F. Haig-Brown records a temperature of 105° F., and Davis saw a temperature of 106° F. in a boy with a livid rash, convulsions and rapidly running pulse.

The fever is, as a rule, proportionate to the extent and severity of the eruptive and catarrhal symptoms.

There is no febrile course which occurs with any degree of constancy. The evening temperature is, however, usually 1° or 2° F. above the morning. Most cases of rubella will exhibit slight fever, varying between 99° and 101° F. In most of our cases the temperature registered 99° or 100° F. In 2 patients it reached 102° F.

It is not surprising that some of the older writers should have regarded rubella as a hybrid of measles and scarlatina, for we commonly note in this disease the catarrhal symptoms of the former and the angina of the latter, but both in very mild form.

Eyes.—The catarrhal symptoms commonly affect the eyes, nose, throat and bronchial tubes. The eyes are commonly seen to be "watery" or slightly injected. Our experience coincides with that of Griffith, who observed this symptom in about one-half of his cases. It is uncommon to find conjunctivitis and photophobia as pronounced as it is seen in measles.

Sneezing.—Sneezing is a frequent symptom, although the paroxysms may be but few and limited to the first day of the eruption. In none of our cases did we note any distinct discharge from the nose; nevertheless, *coryza* is recorded as occurring in a considerable proportion of cases in some epidemics.

Cough.—Cough occurs in a variable proportion of cases, depending upon the character of the prevailing epidemic. When it is present it is usually slight and in no sense comparable with the severe cough of measles. It was absent in the vast majority of our cases. Griffith says a loose, bronchial cough was frequently present in his cases and occasionally demanded treatment. In the severe epidemic observed by Edwards cough was generally present, increasing in frequency and severity and occasionally becoming laryngeal. In quite a large proportion of these cases bronchitic rales, more or less diffused, were heard. The cough lasted about as long as the eruption, so that it had entirely disappeared about the fourth or fifth day.

Sore Throat.—Sore throat of a mild character is an extremely common symptom of rubella. The angina is much milder than that observed in scarlatina, and often does not lead to complaint on the part of the patient. Without inspection it would, doubtless, be frequently overlooked. The congestion is most pronounced upon the upper portions of the anterior pillars. Occasionally a more serious involvement of the throat is encountered, characterized by enlargement of the tonsils, swelling of the pharyngeal mucous membrane and painful swallowing. Mild angina is regarded as a rather constant symptom by most writers.

We have frequently seen upon the *soft palate* a number of pin-head-sized, glistening, reddish elevations. Similar reddish spots have been observed by Emminghaus, Nymann, Gerhardt, Picot, Parke, Dunlap, Kassowitz, Cuomo and Griffith. Forchheimer regards as a characteristic exanthem "the small, discrete, dark-red, but not dusky papules" which are seen early on the soft palate and which disappear in twelve to fourteen hours.

We have carefully examined the *buccal mucous membrane* in a number of cases and have frequently noted the presence of discrete, pin-head-sized, deep-red spots, bearing a considerable resemblance to the macules upon the cutaneous surface. We have never seen the central bluish-white dots which Koplik describes as characteristic of measles.

Hoarseness.—Hoarseness, usually mild but occasionally severe, has been mentioned by Thomas, Emminghaus, Griffith, Aitken, Cheadle, Patterson, Edwards and others. The catarrhal symptoms sometimes subside after a duration of a day or two, but more commonly disappear with the eruption. Occasionally a certain amount of cough may continue for some days.

Tongue.—The tongue is usually covered with a thin, grayish coating, the tip occasionally exhibiting some prominence of the papillæ. While a few writers (Balfour, Hemming, Tripe, Murchison, Burnie and Tompkins) claim to have seen the typical "strawberry" tongue in rubella, this condition must be regarded as exceptional. In some cases the tongue is clean and presents no deviation from the normal appearance. In severe cases Edwards states that the tongue may be dry and brown.

Lymphatic Glands.—Enlargement of the lymphatic glands has long been regarded as a symptom of considerable diagnostic importance. Nearly all writers are agreed as to the constancy of this adenopathy. It must be remembered, however, that a general glandular intumescence occurs in scarlet fever and to a lesser extent in measles, and that lymphatic enlargement, therefore, does not specially differentiate rubella from these diseases.

According to Griffith, J. F. Meigs regards the enlarged postauricular gland as one of the most prominent diagnostic signs of rubella.

It is claimed by some writers (Squire, Thierfelder, Glover, Jalland, Strover, Hardaway) that the glands increase in size often before the appearance of the rash. In other cases, however, the glandular tumefaction may not be noted until the second day after the appearance of the eruption. The glands behind the ears and those lying posterior to the sterno-cleido-mastoid muscles are those most frequently enlarged, although other glands, such as the inguinal and axillary, may participate in the process. Kassowitz found lymphatic enlargement in but one-third of his cases, and Eustace Smith observed it only in certain epidemics.

Nausea.—Nausea and vomiting are rare symptoms in cases of the average type. In severe cases, however, emesis may be severe and persistent. In one of our cases the vomiting continued for several days before the appearance of the eruption, the patient being unable to retain any nourishment at all. Edwards states that in a severe epidemic in the Philadelphia Hospital vomiting occurred in a fair proportion of the cases as the eruption was approaching the maximum. In 5 of these cases it was almost uncontrollable. Griffith observed vomiting on the first day of the eruption in a few severe cases.

The bowels are usually normal or constipated. In a nurse under our care suffering from a very mild attack of rubella, *diarrhea was present* on the first and second days of the eruption.

About 40 per cent of Edwards' cases had gastro-intestinal irritation; this very unusual complication may be accounted for by the severity

of the epidemic. Among these cases were 10 of enteritis and 2 of entero-colitis. Cuomo has also noted the presence of diarrhea in severe cases. Earle encountered 4 cases of intestinal irritation. Balfour found catarrh of the colon a rather common symptom. The majority of make no mention of any disturbance of the bowels.

Itching.—Itching varies both as to frequency and intensity, depending much upon individual peculiarity. It is present in only a minority of cases and is seldom severe.

Pulse and Respiration.—The pulse and respiration usually keep pace with the elevation of temperature. The former may undergo acceleration to 140 or 150 per minute. Edwards says several of his cases presented well-marked symptoms of heart failure, which yielded, however, to appropriate treatment.

The following case of rubella in an adult patient under our care presents many points of interest:

Miss R., trained nurse, aged twenty-seven years, had measles at the age of eight years and scarlatina at the age of six years. Was on night duty in convalescent scarlet-fever ward of the Philadelphia Hospital for Contagious Diseases, in which rubella appeared on March 3, 1903. Patient had been exposed to measles in another building five weeks previously.

March 16: On Wednesday, March 11, the patient was taken sick with headache and sudden vomiting. Since that time she has vomited each day (or rather night, as the patient has continued on night duty, not making known her illness). Emesis occurred five or six times each night. Patient claims to have retained absolutely nothing. There has also been persistent headache, weakness, recurring chilliness, perspiration during sleep and restlessness. No catarrhal symptoms whatsoever; neither coryza, cough nor conjunctival redness.

Although patient had felt feverish for some days, her temperature was first taken on March 15, in the evening, when it registered 102° F. On March 16 it was 100° F. Glands about the jaw and neck are not enlarged.

The eruption was carefully watched for by another nurse who occupied the same bed-room; it was observed at 3 A.M. on March 16, making its appearance first on the legs below the knees, then spreading upward. At 6 A.M. the rash was noticed on the wrists. At 3 P.M. (the hour of our examination) the following notes were made: An eruption of pin-head to lentil-seed-sized, dusky red, slightly elevated macules is seen, quite covering the legs and with even greater profusion the arms. The macules form typical *crescents* on the arms and are also arranged linearly. In other places they run together and present an appearance quite indistinguishable from an intense measles exanthem. The upper part of the chest shows a diffuse scarlatiniform redness. On the back are a number of discrete macules which have just appeared. The face shows no distinct eruption, but the cheeks are quite flushed. The buccal mucous membrane exhibits faint reddish spots.

March 17: The temperature last night was 101.8° F. This morning it is 100° F. The patient is perspiring quite a little. The glands at the angles of the jaw are now enlarged to the size of almonds and are distinctly tender. There is also enlargement and tenderness of the cervical glands. The eruption has become fainter and more confluent on the legs and forearms and has extended to the hands and also from the legs upward to the thighs and buttocks. In the latter region the exanthem is intense and of a morbilliform character. There is more eruption on the back and chest, in which region it has the form of discrete, lentil-seed-sized, sharply defined macules. There is today some macular eruption upon the face. The uvula and soft palate are slightly injected.

March 18: The temperature this morning is 100.4° F. The patient is perspiring and complains of chilliness and pains in the back, arms and legs. The eruption is now faint on the arms and legs, but is still quite conspicuous on the back and chest. The patient vomited last night and again this morning.

March 19: The temperature last night was 101.8° F., and this morning is 100.4° F. Patient is feeling better. The eruption is still well marked on the chest and back, where it shows many crescents. It is more pronounced on the face today than at any previous time.

March 20: The eruption is still present on the back and chest, but is fading. There is still a little fever.

March 21: Temperature last night was 99.6° F. This morning it is 99.2° F. The patient is feeling much better; the appetite is returning. The eruption has practically disappeared.

There were many anomalous features in this attack, among which may be mentioned the long and severe prodromal symptoms, the origin of the eruption on the legs, the complete absence of catarrhal symptoms and the distinctly morbilliform character of the eruption.

COMPLICATIONS AND SEQUELÆ OF RUBELLA.

Rubella and chickenpox rank together as exhibiting the lightest incidence of complications of the various exanthematous diseases. There is no special complication liable to develop during the course rubella, and in the vast majority of cases there are none.

Bronchitis and *pneumonia* have been mentioned by some writers. Edwards saw 3 attacks of pneumonia among 166 cases and Griffith observed 2 in 150 cases. Ryle and Edwards have each reported a case of *pleurisy*. Reference to *enteritis* and *entero-colitis* has already been made. Severe *secondary sore throat* has been reported by Tongue-Smith, Emminghaus and Eustace Smith.

Hatfield reports 2 cases of *stomatitis* and Edwards 4 cases. Earle and Edwards make mention of *aphthæ*, the latter noting it in 30 cases.

Rheumatism was seen once by Slagle and Edwards, and several times by Earle. *Endocarditis* has likewise been observed.

Several cutaneous complications have been recorded. Alexander records 5 cases of facial *erysipelas; urticaria* is mentioned by Slagle, Earle and Cullingworth; *febrile edema* and edema of the legs have been described. *Miliaria, furunculosis* and *pemphigus* have been recorded as rare complications.

Blepharitis, conjunctivitis, phylctenular keratitis and *otorrhea* have been met with. Mettenheimer speaks of *chronic naso-pharyngeal catarrh, permanent swelling of the tonsils* and *gingivitis.* Painful *enlargement of the thyroid gland* was observed by Slagle in 6 cases.

Albuminuria.—Hatfield found albumin in the urine twice and Cuomo three times. Kingsley, Cheadle, Duckworth and Reed each record a case. We noted transient albuminuria in a case of rubella sent into the scarlet-fever wards as a case of scarlatina; the patient clearly had rubella and was discharged in ten days. In an attack of rubella in a girl suffering from postscarlatinal nephritis swelling of the eyelids and legs followed the disappearance of the eruption.

In a series of 166 cases seen by Edwards albuminuria was present in about 30 per cent, but in the next 100 cases but 3 per cent showed albumin. In the first series 9 cases presented well-marked albuminous urine, with dropsy. In none of the cases could tube casts be found.

Most of the complications above described excite interest rather because of their rarity.

Association With Other Diseases.—We observed 100 cases of rubella occurring in children convalescent from scarlet fever. In none of these cases did it occur earlier than the fourteenth day of the disease and usually considerably later. (About one-half of these children had previously in their life had measles.) We have also seen rubella in children convalescing from a mixed attack of scarlatina and diphtheria.

In one little girl still scaling from scarlet fever, and showing the crusts of a profuse chickenpox eruption a well-marked eruption of rubella appeared.

Relapse.—We have never observed a relapse in rubella, and from the absence of reference to such instances on the part of most writers it is evident that such occurrences are uncommon. Nevertheless, competent observers have recorded instances of recurring outbreaks. Emminghaus reports relapses in 3 cases and Earle in 2 cases. Edwards noted it once on the fourth day and once on the twentieth. Griffith noted a recurrence once at the end of eleven days and twice after a period of three weeks. Köstlin, Lindwurm, Golson and Kingsley have also testified to the occurrence of relapses. The recurrent attack may equal the original in the intensity of its symptoms or it may be milder.

There does not appear to be a single authentic case recorded of actual *second attack, i. e.,* due to a second infection and occurring after a period of months or years.

THE DIAGNOSIS OF RUBELLA.

The diagnosis of an atypical case of rubella, particularly when occurring sporadically, may be attended with the greatest difficulty. In its classic form, and especially during epidemic prevalence, the diagnosis is a very simple problem. There is no one symptom which in itself is characteristic; the diagnosis must be made from a consideration of the composite symptomatology.

Measles.—Measles is the disease which bears the closest resemblance to rubella and which has, doubtless, been most often confounded with it. The differential diagnosis between these two diseases may be prefaced by the remark that a morbilliform exanthematous affection occurring as an epidemic among children who have had measles is in all likelihood rubella.

A confusion between measles and rubella may arise when the former disease presents itself in very mild form or when rubella appears, as it sometimes does, with severe manifestations. The history as to the previous occurrence in the patient of measles or rubella is evidence of an important character. It is uncommon for measles to attack an individual twice and still rarer for rubella to act in this manner.

The incubation period of rubella is from five days to three weeks. Griffith regards the variable duration of this stage as compared with the fixed incubation period (about ten or eleven days) of measles as a feature of diagnostic importance.

The prodromal stage is very brief, rarely lasting more than twenty-four hours, or it may be absent altogether. Slight conjunctival redness, sneezing and sore throat may be present. In measles there is a distinct preëruptive stage characterized by considerable fever and marked catarrhal symptoms affecting the eyes, nose, larynx and bronchial tubes. The catarrhal symptoms are more pronounced in mild attacks of measles than in severe attacks of rubella. Some redness of the throat is usually present in rubella, whereas in measles sore throat may be absent.

Pinkish pin-head-sized elevations are at times observed upon the soft palate in rubella. The buccal mucous membrane sometimes exhibits reddish spots. The bluish-red spots surmounted by whitish dots described by Koplik as characteristic of measles are not seen in rubella.

Fever in rubella usually ranges from 99° to 101° F., rarely exceeding this. In measles fever is a prominent symptom, commonly registering 103° F. or more. It is much more protracted in measles than in rubella.

The eruption in rubella spreads more rapidly, fades on one part while spreading to another, and is of brief duration (one to three days). It consists of discrete, pale rose-red, slightly elevated, pin-head to pea-sized macules. In measles the eruption spreads more slowly, reaches a maximum intensity simultaneously all over the body, and

lasts for four or five days or longer, being followed by a staining of the skin. The color is a deep red, at times being bluish. The macules are larger than in rubella, irregularly grouped, often being disposed in and presenting a distinctly blotchy appearance.

Glandular enlargement occurs in both diseases, but is more prominent in rubella, intumescence and tenderness of the postauricular and postcervical glands being frequently present.

Measles is not infrequently complicated by pneumonia, an occurrence which is extremely rare in rubella.

Children with rubella are often so little disturbed as to complain about being put to bed. Measles is accompanied by an amount of prostration and weakness which cause the patients to seek their beds.

The above differentiation will suffice for ordinary cases. We occasionally encounter, however, attacks of measles which present anomalous features. The fever may be extremely slight, the eruption may be poorly marked or the catarrhal symptoms may be almost in abeyance. On the other hand, severe cases of rubella are occasionally met with; conjunctival redness, coryza and cough may be developed to an unusual degree and the fever may be high. In other cases the eruption may be deep red, the macules may be arranged in crescentic groups, the rash persisting for five or six days. We have seen at least one case in which the eruption could not be distinguished from that of measles; in this instance, however, catarrhal symptoms were absent. It is extremely rare to find a case of rubella which in all respects answers to the description of a normal case of measles, and it is still rarer to find a series of cases which fulfil this requirement.

Scarlet Fever.—It is quite possible to confound one form of the eruption of rubella with that of scarlatina. Many writers have acknowledged their inability to distinguish at times between the confluent scarlatiniform type of rubella and the scarlet-fever exanthem. In these cases other symptoms than the skin appearance must be relied upon for the differential diagnosis.

The incubation period of scarlet fever is distinctly shorter than that of rubella, lasting ordinarily from three to seven days. The invasive symptoms are sudden and quite severe; vomiting occurs in the majority of cases, followed by rapid rise of temperature, usually to 103° or 104° F. There is marked sore throat, the tonsils, soft palate and uvula being particularly affected. The glands generally are enlarged, but more especially at the angles of the jaw. The tongue is at first coated, later exhibiting the characteristic red, papillated appearance.

The eruption appears first on the neck and upper chest; the face usually shows the circumoral pallor. The eruption lasts ordinarily five to six days. Desquamation occurring in flakes and most marked on the hands and feet is quite uniform. Middle-ear disease and albuminuria are extremely common complications.

It will be seen that the symptomatology is quite different from that observed in rubella. In the latter disease there is no vomiting, except

in rare cases; the temperature is seldom high; the eruption begins on the face and is of short duration; the "strawberry tongue" is absent; sore throat is usually mild; desquamation when present is branny; complications are extremely rare. In addition, the presence or absence of an epidemic of rubella or scarlet fever will greatly aid in arriving at a correct diagnosis.

In scarlet fever there is a leukocytosis whereas in rubella this does not occur.

Influenza.—Forchheimer states that in the epidemic of influenza in 1892 many cases were observed in which the differential diagnosis between scarlatina, rubella and influenza presented difficulties, at least in the beginning.

There may be present in influenza an erythematous eruption, which may be localized or which may rapidly spread over the body. The fever, prostration, severe gastro-intestinal or respiratory symptoms and the known prevalence of the disease will serve to distinguish it from rubella.

THE PROGNOSIS OF RUBELLA.

The prognosis is absolutely favorable in the vast majority of cases. Deaths have been so uncommon as to attract attention by their rarity; they have invariably been due to complications usually affecting the respiratory tract.

The mortality depends somewhat on the type of the epidemic and the previous condition of health of the patients. Destitute and poorly nourished children are more apt to suffer from complications. Edwards had a mortality of 4.5 per cent among a series of 150 cases occurring in a destitute class in a hospital. There were 5 deaths in 165 cases; 2 died of pneumonia and enteritis, 2 of entero-colitis and 1 of tuberculous meningitis. Among his private cases he never saw a death.

Hatfield records a mortality of 9 per cent occurring among patients in bad sanitary environment. Hemming, Alexander, Cuomo, Slagle, Roberts, McFarlan, Davis and Forchheimer have each reported deaths, the last-named writer as a result of nephritis.

In about 100 cases observed by us in children convalescing from scarlet fever there were no deaths and no complications worthy of mention; indeed, the illness, almost without exception, was of a most trivial character, scarcely necessitating the detention of the children in bed.

THE TREATMENT OF RUBELLA.

What has been said in connection with varicella is equally true of this disease; it is questionable whether it is necessary to isolate rubella patients in their homes. The disease is so mild, and in individuals in average health so devoid of complications and mortality, that such persons might be allowed to take it when it appears in their home. In hospitals it is proper to isolate patients with rubella, for here it may

be inadvisable to superadd to another disease any infectious malady, however mild. The same may be said of institutions in which there are children in depraved health

The only treatment that is necessary in the majority of cases is the guarding of the patient against undue exposure. Where fever is absent and catarrhal symptoms slight, one need not insist on rest in bed, although the child should be kept in a properly heated and ventilated room. The diet should be regulated according to individual requirements. No special medication is required unless the attack be severe or some complication develop.

If it be desirable to protect others from infection the patient should be isolated for about a fortnight.

CHAPTER XI.

THE FOURTH DISEASE? (FILATOW-DUKES DISEASE).

Although great diversity of opinion exists with respect to the existence of this affection as a clinical entity, it would appear to deserve inclusion here until its status is definitely ascertained.

Definition.—The "fourth disease" is alleged to be a contagious eruptive disease characterized by a scarlatiniform eruption with milder symptoms and an incubation period much longer than that of scarlet fever.

In 1885 Filatow, of Moscow, published an article on "rubella scarlatinosa," which he regarded as a separate disease. He further emphasized this view in his lectures on infectious diseases of children in 1896. He stated that rubella scarlatinosa is "a separate acute infectious and contagious disease, which is characterized by a scarlatiniform eruption but which may be separated from scarlet fever by the mild course and especially by the difference in the contagiousness."

His observations were based on a study of 11 cases in one family.

In 1900 Clement Dukes,[1] physician to Rugby School, published a paper, "On the Confusion of Two Different Diseases Under the Name of Rubella;" at this time he gave to the disease in question the name "fourth disease." In 1892 Dukes was consulted about 16 cases of alleged scarlet fever which occurred in a public school. He believed that these cases represented another disease and isolated them merely for fourteen days. Despite this short period of isolation no new infections occurred in the patients' families. Dukes speaks of another epidemic of 31 cases of scarlet fever in a school which were mixed cases of what he later called the "fourth disease." The incubation period of the scarlet-fever cases was two to three days, whereas that of the other disease was fourteen to fifteen days. Nine patients had the "fourth disease" first and then scarlet fever and 1 patient had scarlet fever first and then the "fourth disease." Two of the patients with scarlet fever died. Many of the patients who suffered from the "fourth disease" had previously had attacks of rubella.

Dukes speaks of a further house epidemic of 19 cases of "fourth disease;" 42 per cent of this group were said to have previously had rubella.

THE SYMPTOMATOLOGY OF FOURTH DISEASE.

Prodromal symptoms are usually absent, although occasionally there are observed a slight pain in the throat, or chilliness with nausea,

[1] Lancet, 1900, ii, 89.

headache, backache and anorexia. The incubation period is more like that of rubella than of scarlet fever, varying from nine to twenty-one days. The eruption which consists of small pale red, closely set elements scarcely raised above the skin, is usually the first symptom and may spread over large areas of the body in a few hours. The eruption may also occur on the face, but Dukes states that it is less clear in this region and the nose and lips are exempt. The tongue is coated but the typical "strawberry-and-cream" appearance of scarlet fever is absent. The subcutaneous lymph nodes of the neck are usually swollen and pea-sized but are said not to be as large as the nodes in rubella. The rash fades quickly and is followed by a slight but perceptible scaling. Only exceptionally is the desquamation pronounced. An evanescent albuminuria may be present, but true nephritis is rare.

The temperatures vary in different cases from 37° to 40° C. (98.4° to 104° F.). The pulse is not accelerated except where there is considerable fever.

The infectiousness is trifling at the outset and disappears entirely in two or three weeks. The patient is ready to leave bed in fifteen or sixteen days. Bokay is inclined to recognize the "fourth disease" a special entity and believes that its characteristics are its mild course, the absence of complications and sequelæ, the rapid disappearance of the infectiousness and particularly the long incubation period.

Weaver,[1] Medical Superintendent of the South Borough Infectious Diseases Hospital, supports Dukes' observations, and describes in a number of cases of scarlet fever recurrences with a new eruption and fever. Six such recurrences were observed within three months in 20 cases of scarlet fever. He reports 14 cases in which the "fourth disease" either preceded or followed scarlet fever. The patients had a regular fine punctiform character of eruption, the rash appearing first on the face. There was little or no fever and no general symptoms. There was very slight pharyngitis but no cough or coryza.

Raven[2] reports an epidemic of 12 cases of "fourth disease" in a school of 80 girls, with acute onset, fever from 102° to 104° F., slight vomiting in 2 cases, scarlatiniform rash on the body and legs, scarcely affecting the face; pulse-rate increased only in cases with the highest temperature; pyrexia lasted seven to ten days; the tongue peeled about the fourth day, the glands were not much involved in the early stage except in 1 case, but in this case and 3 others there was secondary enlargement. None of the patients showed symptoms of toxemia. Peeling began on the fourth to seventh day except in one case which never showed this stage. The first cases were diagnosed as scarlet fever, one of the subsequent cases as "German measles." The most probable source of infection was a visit by the whole school to a neighboring town. If so, there was an incubation period of eighteen

[1] Jour. State Med., 1901, **9**, 700.

[2] An Epidemic of "Fourth Disease," Lancet, 1923, i, 950.

to twenty-one days. The points against scarlet fever are: This probable incubation period; no sequelæ or complications except the secondary; a case of German measles among one of the children sent home from the school; also the fact that the epidemic was not more widespread. Against rubella are the following points: Acute onset with high fever; absence of rash from the face; peeling tongue; absence of catarrh. These cases correspond most closely, in the author's opinion, to "fourth disease."

Discussion.—In matters scientific one should have a critical but open-minded judgment.

The descriptions of Filatow, Dukes and Weaver serve to differentiate the disease described from scarlet fever, but in the opinion of the writers rubella has not been definitely eliminated. Indeed, the symptoms depicted would harmonize quite well with the scarlatiniform type of rubella. The only discrepant feature is the history of previous attacks of rubella in a considerable percentage of the patients.

Before definitely accepting or rejecting this disease as a separate affection we require further careful clinical studies and likewise cytological blood examinations and immunological tests.

CHAPTER XII.

ERYTHEMA INFECTIOSUM.

The designation "erythema infectiosum" was first employed by Stricker in describing two outbreaks of a disease in Giessen in 1889 and 1904. The affection was, however, first described by Tschamer, of Gratz, in 1889, under the term of "local rubella." Gumblowitz reported 17 similar cases in 1891, and Tobeitz described cases at the Moscow Medical Congress, under the title of "atypical rubella," at which time Escherich expressed the view that the affection was a separate entity. In 1899 his pupil, Schmid, came definitely to this decision. In the following years numerous communications were published describing the affection under varied names, such as erythema infectiosum febrile, epidemic child erysipelas, erythema simplex marginatum, erythema infectiosum morbilliforme, megalerythema epidemicum, "fifth disease," etc.

Tobler[1] described an epidemic of several hundred cases in Breslau in 1914, of which he himself observed 68 cases.

The condition is undoubtedly communicable, but the conditions under which it is carried are not well known.

The disease has been seen and described chiefly in the Central European countries, and appears to be almost unknown in France, England and the United States.

Brusa thinks that some cases of so-called second attacks of measles were really examples of this disease.

Both children and adults may be attacked, but most cases are observed in the former.

Quite large epidemics have been observed in schools; smaller outbreaks are seen in homes. The incubation period is usually from five to ten days; the widest variations are seven to seventeen days.

THE SYMPTOMATOLOGY OF ERYTHEMA INFECTIOSUM.

Prodromata are usually absent but occasionally coryza, sore throat, photophobia or vomiting are observed. Commonly the rash is the first symptom; it appears at times on the face as a butterfly-shaped patch with the wings on the cheeks. On the forehead and other parts of the face there are outlying erythemato-papular lesions. Where the eruption is pronounced the skin is hot and swollen and firmer than the normal skin. Toward the nose and eyes the redness is rather sharply

[1] Ergebn. d. inn. Med. u. Kinderh., 1915, **14**, 20.

marginated. In some cases it is so pronounced as to suggest a resemblance to erysipelas. The dorsum of the nose and the upper lip are free. The redness gradually pales, but in severe cases it takes on a cyanotic appearance.

The eruption gradually spreads to the extremities and trunk. At times the eruption in these regions may be scarlatiniform or morbilliform, although usually there are patches which during involution acquire a central violet color with circular, annular, gyrate or map-like contours suggesting an erythema annulatum or gyratum. Most patients complain of tension and burning.

The further course of the disease is characteristic. The eruption does not completely clear up after the paling. After a time the skin on the body or extremities acquires a "marbled" or spotted appearance and new ring-shaped lesions are prone to appear.

The duration of the affection is from eight to ten days. Mild cases may terminate in three to four days. On the other hand, Tobler saw a case last twenty days. The lymph glands are not enlarged. The spleen may be swollen. Temperature elevation is slight and of short duration. The leukocytes during the first two days are normal or decreased, after which a leukocytosis of 10,000 to 14,000 cells appears, accompanied by an increase in eosinophiles.

THE DIAGNOSIS OF ERYTHEMA INFECTIOSUM.

The characteristic features are the peculiar redness of the face (butterfly-shaped) without prodromes, the localization and polymorphism of the eruption and the rapid change in the intensity of the same with almost absent mucous membrane and general symptoms. Complications are rare. Berberich observed joint pains in 2 cases, Tripke 2 cases of nephritis and Tobler saw jaundice as a sequel.

Stoose, whose article in Pfaundler and Schlossmann's *Handbook of Children's Disease* (German edition) is the best and most compresive exposition of the subject, concludes that the disease is a *morbus sui generis* and is unrelated to the other exanthemata.

CHAPTER XIII.

TYPHUS FEVER.

Definition.—Typhus fever is a specific, acute, infectious disease, characterized by a continued fever of about two weeks' duration, pronounced nervous and brain symptoms, and by the appearance on the fourth or fifth day of a macular eruption which tends to become hemorrhagic. It is transmitted by the body louse.

Synonyms.—*Spotted fever, petechial fever, ship fever, jail fever, putrid fever, brain fever, camp fever.* Latin, *febris typhus; typhus exanthematicus;* French, *le typhus;* German, *Exanthematischer typhus, Fleck fieber;* Italian, *il Tifo;* Spanish and Mexican, *tabardillo or tifo.*

History.—It is impossible to fix with accuracy the date of origin of typhus fever. The name "typhus" is mentioned in one of the Hippocratic essays, but it was applied at this period to acute fever in general, accompanied by stupor and disturbance of the mental faculties. Many writers are of the opinion that Hippocrates actually observed cases of typhoid fever.

According to Hirsch, the first clear evidence of the occurrence of typhus is given by Fracastorius, a physician of Verona, who carefully chronicled the great pestilence which began in Cyprus and swept Italy on several occasions between the years 1805 and 1830. He distinguished this malady, which he called *morbus lenticularis*, from the plague.

Typhus prevailed in extensive epidemics in different parts of Europe in the seventeenth century. During all this time it was confounded with typhoid fever. Indeed, these two diseases were not generally accepted as separate entities until almost the middle of the nineteenth century.

The Napoleonic campaigns saw thousands of France's soldiers perish by the hand of this ruthless enemy. According to Michaeli,[1] no less than 100,000 Russian soldiers in the Turko-Russian War contracted typhus; of this number, about one-half died. The mortality was particularly high among surgeons, 60 per cent of the stricken succumbing to the disease.

Typhus fever is endemic in the large cities of the central plateau of Mexico; it increases in the winter months and not infrequently assumes epidemic proportions.

Among the most important contributions to our knowledge of the

[1] Quoted by Curschmann: Nothnagel's Encyclopedia of Practical Medicine, American edition, 1901.

disease may be mentioned the writings of Sir John Pringle, Hecker, Rasori, Hildenbrand, Hufeland, Larry, Armstrong, Horn, Roupell, and more recently Murchison, Virchow, Lindwurm, Wood and Griesinger.[1]

In the United States the writings of Gerhard and Pennock[2] are deserving of special praise. Curschmann says: "To two American physicians, Gerhard and Pennock, belongs the credit of having finally established the differentiation (between typhus and typhoid fever). The clearness of their differential diagnostic statements is noteworthy for their time."

Geographical Distribution.—Ireland and England (more particularly the former) have always been the home and distributing center of typhus fever. This pestilence has been almost continuously present in these countries, exhibiting from time to time violent epidemic outbursts. The aggregate loss of life in Ireland from this disease has been appalling. Typhus fever has fortunately declined in recent years.

The Russian provinces bordering on the Baltic Sea and Poland have also been for years typhus-stricken territories.

In Germany the disease is usually limited to the southeastern provinches and to upper Silesia, although in times of epidemic prevalence Prussia also suffers. Germany receives its infection almost exclusively from the Russian borders.

In France typhus fever is seldom widely diffused, although it is said to persist endemically in certain parts of Brittany.

The disease is endemic to a certain extent in northern Italy and also in Sicily and the neighboring islands. During periods of epidemic extension the entire country is overrun, as well as the lower provinces of Switzerland.

Certain districts of what was formerly Austria had its endemic centers in Galicia, Silesia, Moravia and Bohemia. The disease is practically never extinct in Turkey, nor in Persia and China. India is comparatively free from typhus and the northern coast of Africa suffers only at times, with the exception of Algeria, in which country the disease has become endemic.

Spain and Portugal appear to be protected by their peninsular isolation and enjoy a relative degree of freedom from typhus.

Ireland and Russia represent the two important hotbeds of the disease. From these centers the disease is carried from time to time to the central and northern European countries and to America. Irish emigration has frequently brought the disease to New York, Philadelphia, Baltimore and other ports of the United States, but typhus has never gained a permanent footing in this country.

[1] Curschmann gives full bibliographic references to the modern literature of typhus fever, and Murchison the literature before 1865.

[2] On the Typhus Fever which Occurred in Philadelphia in 1836, Showing the Distinction Between It and Dothienteritis, Am. Jour. Med. Sci., 1837, vols. **19** and **20**.

The disease persists endemically in the large cities of the central plateau of Mexico. In these densely populated districts typhus is never absent and epidemic outbreaks occur not infrequently.

Since the World War it has been estimated that 1,000,000 persons have died of typhus fever. In Serbia 135,000 persons succumbed and in Roumania, 200,000.

THE ETIOLOGY OF TYPHUS FEVER.

Typhus fever is an infectious disease due to a specific cause transmitted by the louse.

A large number of various bacteria and especially Bacillus proteus X have been claimed from time to time to be the cause of typhus fever, but at present there appears to be a consensus of opinion that the etiological agent is a minute, intracellular, pleomorphic and faintly staining parasite called Rickettsia prowazeki. The term "rickettsia" is a generic one, selected in memory of the late Dr. Howard T. Ricketts, who died of Rocky Mountain spotted fever while engaged in investigating this disease and in which he discovered a similar agent as the cause.

Rickettsia prowazeki is in all probability a living microbe, although Woodcock[1] states that this has not been proven and suggests that it may be a non-living, transmissible virus of the nature of a cytotoxin or enzyme. Wolbach,[2] in a thorough review of studies bearing upon the etiology of typhus fever, states: "Another factor that must not be lost sight of in a discussion of the etiology of typhus is the property of the blood of typhus patients and convalescents to agglutinate certain strains of proteus bacillus, usually designated as Bacillus proteus X strains. It is well known that the serum from typhus patients agglutinates a number of bacteria and a number of strains of Bacillus proteus; nevertheless, the agglutination of Bacillus proteus X-19 in very high dilutions is almost specific for typhus fever, and is a valuable diagnostic adjunct, and has led workers seriously to consider it as a possible cause of typhus. Some of them have attempted to connect this bacterium with Rickettsia prowazeki. These attempts have led to interesting hypotheses, notably those of Weigl and of Breinl."

Weigl,[3] in 1923, in a preliminary communication, reports astounding results of cultivation experiments performed with typhus-infected guinea-pigs and lice. He concludes that Plotz' bacillus, the Microbion typhi-exanthematici of Barykin and Kritsch, certain bacilli (the As strains) isolated by Kuczynski and the proteus bacillus X strains of Weil are all derivatives of Rickettsia prowazeki, which he accepts as the cause of typhus as it exists in the louse. The form assumed by Rickettsia prowazeki in man, he says, is unknown. Aërobic cultures

[1] Jour. Roy. Army Med. Corp., 1922, **39**, 243.
[2] Jour. Am. Med. Assn., 1925, **84**, 726.
[3] Ztschr. f. Hyg. u. Infectionskr., 1923, **99**, 303.

from typhus-infected guinea-pigs yielded him Bacillus proteus X strains, anaërobic cultures yielded Plotz' bacillus and "intermediate forms" like the organisms of Barykin and Kritsch and Kuczynski. Weigl also states the Bacillus proteus X strains developed in suspensions of Rickettsia prowazeki made from lice, though such suspensions have lost their virulence and were sterile for a period before the proteus organisms made their appearance. He regards the Bacillus proteus X strains as mutants or atavistic throwbacks ("atavistischer Rückschlag") of Rickettsia prowazeki.

Breinl[1] also accepts Rickettsia prowazeki as the cause of typhus as it appears in the louse. Bacillus proteus X-19 he regards as the cultivatable non-virulent form, while this microörganism in the mammalian host exists in a form not yet demonstrated, either because of its small size or because of refractory staining properties. Wolbach then summarizes the evidence for the etiological relationship of Rickettsia prowazeki to typhus as follows: "(1) The occurrence of the microörganisms in the lesion of the disease; (2) their occurrence as the sole distinctive acquisition of lice nurtured on typhus patients; (3) the failure to separate Rickettsia prowazeki from the virus of typhus by any method yet employed; (4) the cultivation of Rickettsia prowazeki in lice by the method of intestinal tract injection under conditions which virtually make the louse a living culture tube; and (5) the cultivation of Rickettsia prowazeki in tissue-plasma cultures, using as a source of the virus a strain maintained for three years by continuous passage through guinea-pigs.

"This evidence ignores the role of Bacillus proteus X strains. It must be remembered that there are only a few cultures of this organism that are suitable for the agglutination test of typhus, and that these organisms have all been isolated from the urine of typhus cases, and there is no evidence that Bacillus proteus X-19 invades human tissues. Breinl himself states that the presence of Bacillus proteus in typhus is a matter of coincidence only. It seems more reasonable to explain the agglutination of these rare cultures by typhus serum on other hypotheses than that they represent mutants of Rickettsia prowazeki. I do not know what to say to those who, in the face of the evidence I have assembled, may still insist that Rickettsia prowazeki is not the cause of typhus, but simply invariably accompanies the virus of typhus, particularly to those who assume, like Breinl and Weigl, that the virus of typhus in man may be in ultramicroscopic form. The same line of reasoning may be applied to all infectious agents, whether or not cultivated in test-tubes. Rickettsia prowazeki has not been demonstrated in the circulating blood with certainty. It can, however, be found in the lesions of the disease in man and in tissue-plasma cultures. I fail to see good reason for assuming a form to exist in the blood outside the morphological range of Rickettsia prowazeki with

[1] Arch. d. l'Pasteur, 1924, **13**, 208.

which we are familiar. The evidence for causal relationship of Rickettsia prowazeki to typhus is now so complete that it is necessary to elaborate complicated hypotheses to account for the facts on any other basis than the one simple explanation, which is that Rickettsia prowazeki is the cause of typhus."

Maxcy[1] states that the conditions usually accepted for transmission of the Old World form of typhus fever are as follows:

1. The virus exists in Nature only (*a*) in the blood and tissues of infected human beings, and (*b*) in the bodies of lice which have fed on such persons.

2. Man is infective for the louse only for a brief period; namely, from the onset of the disease until defervescence has been established, a matter of two or three weeks.

3. One attack in man confers a definite, high and durable immunity.

4. The louse, having bitten an infective man, after a period of five or six days is capable of conveying the infection to other persons by its bite.

5. The louse remains infection during the remainder of its life, a matter at most of two or three months (Nutall, 1917).

6. Almost all attempts to demonstrate the inheritance of infectivity in the louse have failed.

Arkwright and Bacot,[2] the latter losing his life a martyr to his investigations in this dreadful disease, state that the excreta of infected lice may transmit the virus as well as their bites.

IMMUNITY IN TYPHUS FEVER.

The disease occurs spontaneously only in man; experimentally it has been successfully transmitted to some of the monkeys and probably to guinea-pigs. There are no evidences of racial immunity—all persons, irrespective of race, age and sex appear to be extremely susceptible and especially if the general health and resistance have been undermined by privation, disease and general misery.

One attack of the disease generally confers an immunity for the balance of life and there is some evidence to the effect that the serum of a recovered individual may prove effective in the treatment of the disease, suggesting the presence of immunity principles in the blood for a short time at least after recovery.

Weil-Felix Agglutination Reaction in Typhus Fever.—As the subject stands today it would appear that during typhus fever there may be the production of agglutinins for Bacillus proteus and other bacteria, but especially for strain X-19 of Bacillus proteus, and that the agglutination test with this organism yields reactions of diagnostic value. Wolff[3] has recently subscribed to Epstein's theory that Bacillus pro-

[1] Pub. Health Repts., 1926, **41**, 2967.
[2] Brit. Jour. Exper. Path., 1923, **4**, 70; 1922, **3**, 196.
[3] Berl. klin. Wchnschr., 1920, **57**, 834.

teus vulgaris, originating in the intestinal tract, undergoes, through symbiosis with the typhus virus, a change in its internal structure and becomes agglutinable by the serum in typhus fever. The reaction is not specific and requires more investigation for establishing its exact status.

In applying the agglutination test for diagnosis the dilutions should range from 1 to 20 upward; agglutinating at 1 to 20 is regarded as suspicious. In typical cases agglutination may occur in dilutions as high as 1 to 250 to 1 to 1000. Agglutinins are first detected about the sixth day of the disease and rapidly disappear after the crisis.

Vaccination Against Typhus Fever.—Unfortunately there is not as yet any efficient method for vaccination or active immunization against typhus fever. The specific etiological relationship of the Plotz bacillus to the disease lacks confirmation and the prophylactic value of its vaccine is very doubtful. As previously stated, one attack of typhus fever generally protects for the balance of life. Apparently immunization requires the activity of living virus, as Mollers and Wolff[1] were unable to vaccinate with heat-killed virus. The results obtained by Mitchell and Richardson[2] by injections of 1, 2 and 3 cc. of sterile defibrinated typhus blood are suggestive of successful active immunization, but inconclusive.

TRANSMISSIBILITY OF TYPHUS FEVER.

Typhus fever is an extremely transmissible disease, resembling to a limited extent the eruptive affections, such as measles, scarlet fever and smallpox. Inasmuch as it is accompanied quite constantly by a cutaneous eruption of uniform character, there is good reason to include typhus among the exanthemata.

While typhus is an extremely transmissible disease, its infection is not so readily conveyed to others as is that of measles or smallpox. The chances of contracting the disease are directly proportionate to the frequency, duration and intimacy of the exposure and to the presence or absence of certain sanitary safeguards.

While the disease may be acquired after a very brief contact, experience teaches that the frequency and duration of the exposure exert a considerable influence upon the chances of infection. Nurses who are continuously and intimately in attendance upon the sick run the greatest risk. During the Crimean War, within a period of fifty-seven days, 603 nurses out of 840 in the service contracted typhus. In the Turko-Russian conflict all of the Sisters of Charity and 80 per cent of the orderlies were attacked.[3]

The incidence of typhus in hospitals is greatest among nurses, next among resident physicians and students, then among visiting physi-

[1] Deutsch. med. Wchnschr., 1920, **46**, 484.
[2] Lancet, 1920, i, 742.
[3] Mentioned by Licéaga: Loc. cit.

cians and, finally, among officials who make but occasional visits. This is now readily comprehensible since the more intimate and frequent the contact, the more likely is the infected louse to be transferred to the exposed person.

Anderson[1] states that at the Fever Hospital at Glasgow, and in the English Fever Hospitals generally, the assistants rarely escape the disease.

Stokes and Cusak[2] are authority for the statement that from 1813 to 1846 in Ireland there were among physicians 568 cases of typhus and 132 deaths, constituting approximately 46 per cent of all cases and 10.5 per cent of the deaths. Sixty per cent of the surgeons in the Russo-Turkish War were stricken by the disease.

That the infection is frequently resident in the underclothing is proven by the frequency with which washer-women, who have cleansed the bed and body linen of typhus patients, have contracted the disease. Indeed, the number has been so great in some epidemics that women could no longer be secured to undertake this work. This observation was made before the louse was known to be the carrier of the infection.

Epidemics of typhus are much more common in the cold than in the warm months. In Mexico and other countries in which the disease is endemic, epidemic recrudescences occur during the *winter* season. Curschmann regards the winter outbreaks as a result of the mode of living at this time of the year.

But few persons seem to possess a natural immunity against typhus. The vast majority of persons will when intimately exposed contract the disease.

One attack of typhus protects against subsequent attacks in the majority of cases. There are, to be sure, exceptions which occur about as frequently as in the other exanthematous diseases.

Sex.—Sex appears to exert but little influence upon susceptibility to the disease.

Age.—Typhus attacks persons of all ages, except possibly infants at the breast, who exhibit about the same degree of insusceptibility to this disease as to the other exanthemata.

The disease is most common in youth and in early and middle adult life, from the ages of ten to forty years. The very aged are not spared, for persons over the age of eighty years are every now and then attacked.

Overcrowding.—Overcrowding plays an important part in the spread of typhus fever. Therefore, the disease commonly breaks out in prisons, barracks, lodging-houses, ships and badly constructed hospitals. The two English cities which are most densely populated, and in which people are most crowded in restricted quarters, are Liverpool and London, and these cities are those which habitually have most typhus.

Susceptibility to typhus fever is greatly increased by debilitating

[1] Quoted by Licéaga.
[2] Ibid.

influences, which lower the resisting power of the individual. Physical exhaustion, mental anxiety, intemperance, underfeeding, exposure and all the accompaniments of poverty and misery are included in this category. In addition, various acute and chronic diseases may act as strong predisposing causes.

Typhus fever more than any other disease follows in the path of war and famine; it is essentially a disease of the poverty-stricken and miserable.

THE PATHOLOGY OF TYPHUS FEVER.

Contrary to the statements of some of the older writers, there is nothing pathognomonic or characteristic of typhus fever in the autopsy findings. Such changes are present as would indicate the existence of an intense infectious process. Postmortem results in typhus fever often have a negative value in excluding the possibility of the existence of typhoid fever.

When death occurs during the eruptive period there will often be seen the petechial spots, which, according to their age, will present purplish, greenish, yellowish or brownish coloration.

Where considerable ecchymotic exudation into the skin has occurred incision through the patch will show the presence of blood in the corium. Occasionally hemorrhages take place into the muscles, later giving rise to circumscribed areas of necrosis and softening.

The severe cerebral symptoms might lead one to expect pronounced changes in the *nervous structures*. Nothing, however, peculiar to the disease is observed in the brain or its membranes. The meninges are usually the seat of marked congestion and not infrequently of hemorrhages, which may be extensive, although they are usually circumscribed. Diffuse meningitis is a condition seldom encountered. The surface of the brain is hyperemic and the cerebral substance upon section shows numerous dots of blood. The cortex of the brain is rather softer than normal and slightly edematous. A subarachnoid effusion is nearly always present, being clear, turbid or sanguinolent in character. The same is true of the ventricular fluid, which is not infrequently increased in amount.

The spinal cord shows congestion of the pia mater and effusion into the subarachnoid space.

The changes in the *cardiovascular* apparatus are the same as those observed in other infectious fevers. The heart muscle is soft, flabby and of a pale or yellowish-red color, indicating myocardial degeneration. One-sided dilatation of the heart is usually present. Endocarditis and pericarditis are of great rarity.

At times structural changes in the bloodvessel walls are noted. Not rarely thrombi are found adherent to the walls of the bloodvessels of the thigh. Embolic or thrombotic obstruction of the arteries of the extremities is occasionally noted, giving rise to gangrene of the parts supplied by the damaged vessels.

The frequent employment of venesection by the older physicians gave repeated opportunity for the study of the coagulability of the blood in typhus fever. The blood is darker than usual and shows a less tendency to coagulate than under normal conditions. Jiminez described the blood as resembling "a watery fluid holding in suspension a very fine powder of a dark-red color."

The *respiratory organs* are commonly the seat of pathological changes. The mucous membrane of the nose, pharynx and larynx is congested, swollen and often macerated. Ulcerations with formation of pseudo-membrane may be seen in the pharynx or larynx and, in rare cases, farther down the respiratory tract. Curschmann found intense laryngeal disease in 4 per cent of the case at autopsy. There was "marked reddening and swelling of the mucous membrane, with edema and erosions or fissures, the last particularly on the posterior wall, on the epiglottis and on the ventricular bands."

Unilateral perichondritis and necrosis of the arytenoid cartilage were associated with these changes. The trachea, bronchi and bronchioles show evidence of severe catarrhal inflammation; the lining membrane is reddened, soft and covered with an adherent, tenacious mucus.

Hypostatic congestion of the base of the lungs is extremely common; the pulmonary tissue in this condition is devoid of air, no longer crepitates or froths and is practically in a state of splenization.

Lobar pneumonia is common in some epidemics and rare in others; Curschmann says 15 per cent of his autopsies discovered the presence of lobar pneumonia, and Licéaga reports 7 cases of extensive pneumonia out of 21 examined. Hemorrhagic infarcts and gangrene of the lungs are at times observed.

Pleurisy is comparatively uncommon; when it develops it may eventuate in empyema.

The chief interest in the alterations in the *digestive tract* attaches to the appearance of the intestinal mucous membrane. Many of the descriptions by the older writers of the ulcerations found in the bowel related really to cases of typhoid fever which were erroneously diagnosed.

In typhoid fever Peyer's patches are hypertrophied and ulcerated, the excavations at times extending to such depth as to lead to perforation of the bowel and the development of peritonitis. In typhus fever Peyer's patches are not involved, and the solitary follicles are likewise usually exempted. The mucous membrane is congested and occasionally punctated hemorrhages into the mucous membrane are noted.

The *stomach* is occasionally congested and may exhibit small hemorrhages into the walls; in rare cases there is ecchymotic extravasation and extensive softening.

The *liver* is often enlarged and hyperemic and shows evidence of cloudy swelling.

The *spleen* is enlarged in a considerable proportion of cases, but the

swelling is neither as pronounced nor as uniform as is the case in typhoid fever.

The *kidneys* frequently show evidences of congestion and cloudy swelling. Curschmann states that in the Moabit Hospital in Berlin, in 1878 and 1879, there were found 5 cases of pronounced recent parenchymatous nephritis among 80 autopsies.

THE SYMPTOMATOLOGY OF TYPHUS FEVER.

Period of Incubation.—The period elapsing between the reception of the poison and the true onset of the disease is usually devoid of symptoms. In a minority of cases mild manifestations of indisposition may be noted, such as *malaise*, loss of appetite and vague aches.

It is somewhat difficult to accurately estimate the duration of the incubation stage, for persons do not always take typhus upon the first exposure. It is only when the contact has been single and brief that the length of the latent stage may be satisfactorily determined. Of course, every possibility of exposure to another source of infection must be excuded.

The average length of the period of incubation may be said to be *twelve days*. In a not inconsiderable number of cases it will be found to be four or five days less than this. The extreme limits of the period may vary from one, two or four days to about two weeks. Much longer periods, extending to several months, have been mentioned by the older writers, but these have doubtless been based upon errors of observation.

General Outline of the Symptoms.—The invasion of typhus is usually sudden and not heralded by prodromal illness. An abrupt rigor or a succession of chilly sensations marks the onset of the febrile period. Chilliness may persist for several days, seldom amounting, however, to visible shivering. Nausea and vomiting are not infrequently present, but seldom continue long. Constipation exists in the vast majority of cases. The fever mounts rapidly and to a considerable height; ordinarily, the initial pyrexia registers 102° or 104° F. With the rise in the temperature there develop the usual associated symptoms of high fever—headache, vertigo, insomnia, muscular pains and prostration. The headache, which is severe and unremitting, is usually located in the frontal and temporal regions, with often pronounced pain and tenderness in the eyeballs. Backache, chiefly in the sacral region, is sometimes a distressing symptom. Pains in the legs are not uncommon.

A frequent early symptom is *nose-bleed*, which is observed most commonly about the third day. It may vary in severity from a barely perceptible bleeding to an uncontrollable and even fatal hemorrhage, as in a case observed by Jiminez.

Tinnitus aurium is often pronounced, followed later by partial or

complete deafness. The mind is usually clear in the beginning, although the patient exhibits but little interest in his surroundings.

The *facies* is so characteristic as to be of diagnostic value. The face is flushed, dusky and sometimes slightly edematous; the eyes are congested and heavy, and the expression dull and apathetic. There is evidence of great muscular relaxation, the patient lying prostrate upon his back. Sleep is interrupted by disturbing dreams, which cause the sufferer to start.

The temperature now continues its ascent, reaching its acme about the fourth or fifth day. With the increased pyrexia there is a corresponding augmentation of the pulse-rate, which commonly reaches 100 to 120; in children the pulse is more rapid, acquiring a frequency of 140 or 150 to the minute.

About the fourth or fifth day the most characteristic symptom of the disease—the rash—makes its appearance. The true exanthem is, in some cases, accompanied or preceded by a morbilliform rash of transitory duration, analogous to the prodromal rashes of variola, vaccinia, etc. The typhus eruption is commonly seen first on the anterior surface of the trunk, and later on the back, arms and legs. The face and palmar and plantar surfaces are usually exempted. The eruption consists of pin-head- to lentil-seed-sized, reddish spots, or macules. These acquire from day to day a deeper coloration, finally becoming purplish and no longer disappearing under the pressure of the finger, thus evidencing a hemorrhagic extravasation into the skin. The number of lesions is at first small, but later the eruption may become quite profuse.

The full development of the exanthem marks the height of the morbid process. The symptoms have now acquired increased severity. The fever is at its maximum and the pulse is rapid; the tongue is parched, dry and brown; the mouth half-open, the teeth covered with sordes and the lips with blood crusts. A dry cough denotes the presence of a bronchitis, and rales may be heard upon auscultation. Catarrhal inflammation of the larynx may lead to hoarseness or aphonia.

The patient is profoundly prostrated, the lips scarcely moving on speaking. Apathy has been replaced by a delirium which in some cases is of a muttering character, but in others is violent or maniacal. Homicidal or suicidal efforts may be attempted and require the greatest vigilance upon the part of the attendants.

The patient is unable to hear, speaks in a scarcely audible tone and is often too weak to protrude his tongue. Delirium, stupor and semi-consciousness follow each other in irregular order. The abdomen is tense and somewhat tympanitic; constipation is the rule, but diarrhea may set in toward the end of the disease, and the stools may be passed involuntarily. The bladder becomes paralyzed and incontinence or retention results. If the disease progresses to an unfavorable termination the temperature increases to 105° or 106° F., the pulse becomes

rapid and feeble, the face acquires a livid hue, there is picking at the bed-clothes and tremor of the hands, increasing coma, and finally death from exhaustion.

Death may also result from the effects of wild delirium and physical exhaustion; in other cases a bronchopneumonia or hypostatic congestion of the lungs hastens the fatal outcome.

Recovery may occur in typhus fever even after the development of alarming symptoms. The disease is self-limited and not of protracted duration, and if the patient can be tided over the crucial stage rapid convalescence sets in.

When a favorable termination is to occur a rapid defervescence in the temperature is noted about the fourteenth day; with the fall in the fever the patient lapses into a refreshing slumber. The pulse diminishes in frequency and acquires more volume, the tongue becomes moist and loses its coating, the mental faculties clear up, the voice returns and the patient expresses a desire for some food. The eruption gradually fades in color, the petechial lesions being last to disappear. Branny desquamation usually occurs at the site of the purplish maculæ and stains persist for a considerable length of time.

Deafness and prostration may continue for a while, but recovery from moderate cases of typhus is more rapid than would be expected from the formidable character of the symptoms.

Consideration of the Symptoms in Detail.—**Fever.**—The intensity of the fever in typhus is an excellent index of the severity of the disease. The febrile curve has certain distinct characteristics which distinguish it from typhoid fever.

The pyrexia rises quite rapidly to a considerable degree, so that on the evening of the first day the temperature registers 102° or 103° F. and occasionally 104° F. Some of Wunderlich's cases exhibited temperatures from 104° to 104.9° F. With slight morning remissions the fever continues its ascent on the second and third days, commonly reachings its maximum on the evening of the fourth. At this time the evening temperature in cases of moderate severity will be in the neighborhood of 104° F., whereas in very severe attacks it may reach 105° or 107° F. The fever now remains at about the same level for four or five days, although a slight lowering of the temperature may be noticed in the evenings. From the seventh to the ninth days an average evening temperature of 103° to 105° F. might be expected.

In favorable cases the fever begins to decline on the ninth, tenth or eleventh day or a little earlier or later. In severe cases it may be postponed until the fourteenth, fifteenth or sixteenth day. In desperate cases the fever may rise to great height about this period.

A day or so before the subsidence of the fever it is not rare to observe striking irregularities in the temperature curve. This precritical disturbance is sometimes characterized by a pronounced rise in the temperature to 105° or 106° F., and in other cases by a fall to normal or thereabouts. There is, however, a rapid rebound and the fever

shortly afterward permanently abates. The fall in the temperature commonly begins in the evening and continues during the night. Critical declines may occur in some cases, the temperature dropping

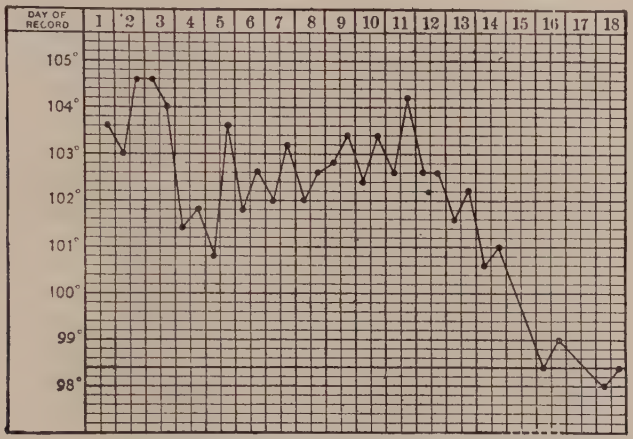


FIG. 123.—Case of typhus; gradual decline of temperature. Recovery. (Doty.)

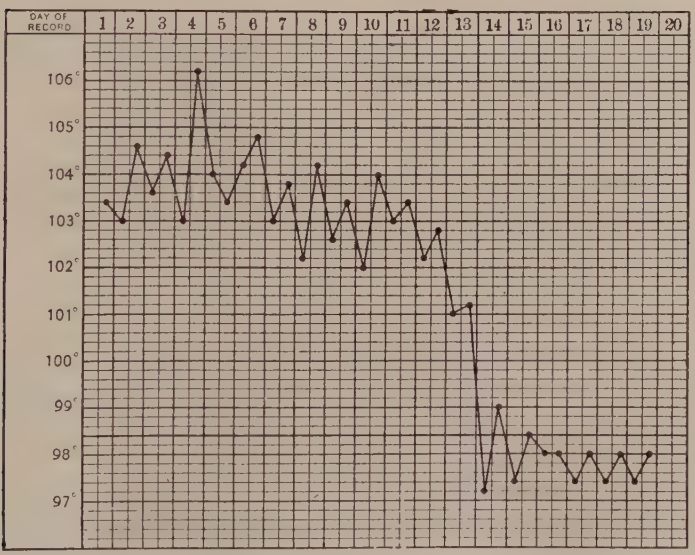


FIG. 124.—Case of typhus; decline of temperature by crisis. Recovery. (Doty.)

to normal in the course of twelve hours; more commonly, however, there is a step-like descent, requiring two, three or four days to reach the normal line. It is seen, therefore, that the fever more often declines by lysis than by crisis (Fig. 124).

In fatal cases it is not rare to note a preagonic hyperpyrexia. Wunderlich observed a temperature of 109.4° F. just before death.

Pulse.—The frequency of the pulse in typhus fever, under ordinary circumstances, is proportionate to the intensity of the accompanying pyrexia. In this respect and in the rarity of dicrotism it differs from the pulse of typhoid fever. In moderately severe cases the pulse-rate in the evenings, during the first week, varies from 110 to 120. At this time the pulse is full and of good volume, but later becomes softer and more compressible. Dicrotism is occasionally observed during the second week, but is distinctly rarer than in typhoid fever. In severe cases, as the disease progresses, the pulse becomes rapid, feeble and small and frequently intermittent. Patients may lie for a number of days with the pulsations scarcely palpable at the wrist.

The cardiac sounds are clear and of good tone early in the disease, but later, especially in severe attacks, give evidence of myocardial change. They may become weak and distant and the first sound almost inaudible. When this develops with accompanying cyanosis of the face and extremities acute dilatation of the heart is to be expected.

The Typhus Rash or Exanthem.—The eruption of typhus fever is so uniformly present and so characteristic of the disease as to warrant the inclusion of typhus in the list of exanthematous affections. It may in rare cases be absent, and in others so poorly defined as to escape observation. It has been estimated, however, that it is seen in 95 per cent of all cases. It is one of the most conspicuous and diagnostic symptoms of the disease, a fact which has led to the use of such designations as "spotted fever," "petechial fever," etc.

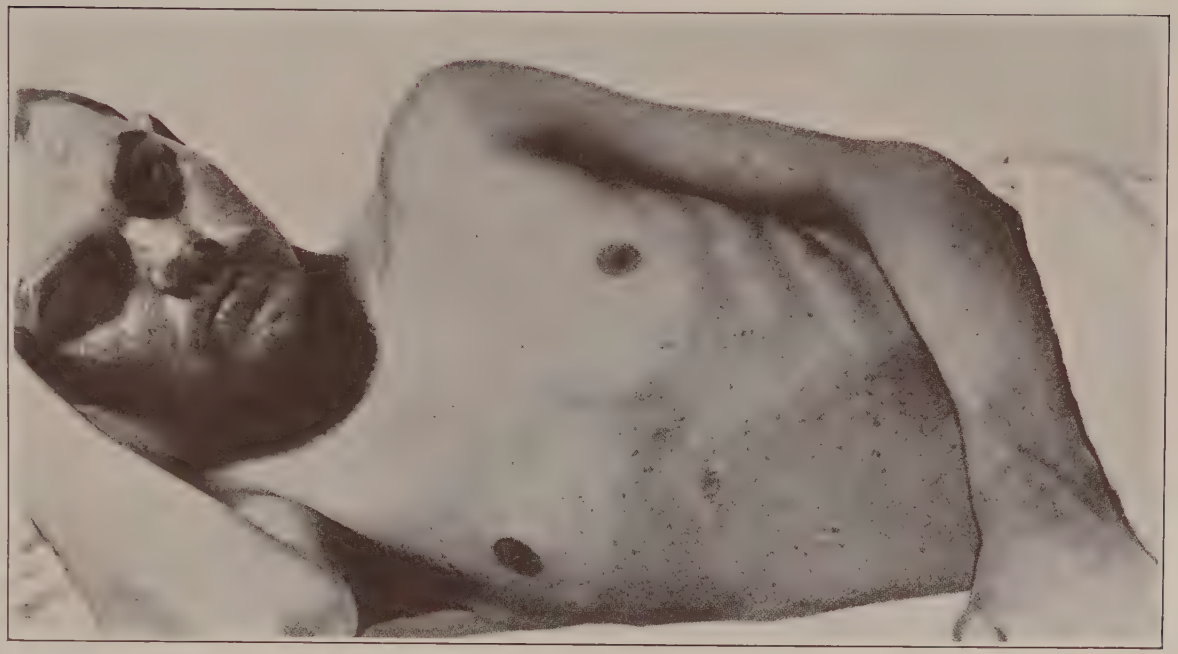
The exanthem usually makes its appearance upon the fourth or fifth day of the disease, but may occur as early as the second and as late as the eleventh day. Salamon, working with Curschmann, observed the rash in 39 cases of typhus; of this number, it appeared 11 times on the fourth day, 13 times on the fifth day and 5 times on the seventh day.

The spots appear first upon the abdomen, chest, shoulders and back; very soon they make their appearance upon the arms and legs, even as far as the hands and feet. The face is usually entirely free of eruption, although in children at times the rash may be sufficiently pronounced to cause confusion with measles.

The lesions are not very abundant upon the first day, but constantly increase in number for about forty-eight hours, when the full complement of spots is present.

The rash is made up of two elements—a background consisting of a poorly defined, violaceous reticulation, the so-called "subcuticular mottling," and the rose spots or maculæ. The macules are pin-head- to lentil-seed-sized, pale red or rosy-red at the onset, with ill-defined borders and scarcely elevated above the surface of the skin. In some cases the mottling may be present without the spots, but the converse of this is seldom the case. In the beginning the macules disappear

PLATE XXIV



Petechial Eruption of Typhus Fever upon the Trunk. Recovery.

Patient was an immigrant treated in the Municipal Hospital.

completely upon pressure, but gradually the color becomes more dusky or actually purplish and the discoloration can no longer be made to fade under tension or pressure. The bluish or purplish coloration is evidence of hemorrhagic extravasation into the skin. At times, late in the course of the disease, petechiæ may develop upon healthy areas of the skin without the previous presence of macules.

Only a certain proportion of rose spots become the seats of hemic extravasation. In general, it may be stated that the greater the extent of hemorrhage into the skin, the more severe is the attack. Petechial spots are most commonly seen about the flexures of joints, particularly the groin, and on dependent portions of the cutaneous surface, such as the back.

The duration of the eruption varies according to the amount of dermic hemorrhage. Simple rose spots may disappear in a day or two; those showing moderate extravasation fade in five or six days, while deep purplish petechiæ may persist for two or three weeks.

During the process of fading the spots pass through the color gradations of blood pigment, showing themselves as greenish, yellowish or brownish stains. The disappearance of the eruption is commonly followed by a branny or furfuraceous scaling.

The individual lesions of the typhus eruption in the beginning bear a strong resemblance to those of typhoid fever. They are, however, less papular, more abundant, and later petechial in character. The macules are, at times, more abundant upon the extremities than upon the trunk, a circumstance that is never observed in typhoid fever; indeed, in the latter disease spots upon the arms and legs are quite unusual.

In exceptional cases the rash of typhus may be absent, constituting the so-called *typhus sine exanthemate*. Murchison failed to discover a rash only 55 times in 2499 cases.

Spleen.—The spleen appears, according to Curschmann, to be moderately enlarged in the majority of cases of typhus. The enlargement begins usually from the third to the fifth day and is determinable by palpation. The splenic swelling does not last long, but subsides usually with the decline of the fever. This explains the negative results that have been noted in autopsies, the swelling having disappeared before death.

Subcutaneous Lymphatic Glands.—The subcutaneous lymphatic glands are ordinarily not enlarged. In some epidemics the inguinal and axillary glands have been observed to undergo inflammation and suppuration. The parotid and submaxillary glands may become tumefied either early or late in the course of the disease.

Nervous System.—Psychic disturbances in typhus fever are among the most conspicuous and constant manifestations of the disease. Indeed, the word typhus is derived from a Greek term signifying stupor. Early in the disease the nervous phenomena play a prominent role in the symptom-complex.

Headache, intense restlessness and insomnia are seen in nearly all cases. The cephalalgia is intense and persistent, seldom abating before the appearance of the exanthem and frequently not until the end of the first week. Inability to sleep is a distressing symptom and one difficult to relieve; it often continues up to the critical period, when the patient falls into a refreshing slumber. Giddiness and noises in the ears commonly accompany the early headache; the former is rendered manifest when the patient assumes the erect position or even when he sits up in bed.

Consciousness is preserved during the early days of the disease, but there is a dulling of the mental faculties. The patient, though listless and apathetic, is able to pertinently answer questions addressed to him.

Gradually, however, the intellect becomes clouded, perception is slow, memory fails and confusion reigns supreme. The patient loses knowledge of his surroundings and lapses into a semi-stuporous condition from which he can be but partially aroused.

As would be naturally expected, the headache, rachialgia and other subjective disturbances gradually disappear as the psychic faculties are obtunded.

Delirium is a prominent symptom of the disease and usually manifests itself during the latter half of the first week. It varies greatly in its character, depending much upon the temperament of the patient and the nature of the psychic impulses which he experiences. At times it is of a muttering character, the patient talking incessantly in a low tone between his half-closed teeth. The sufferer frequently imagines himself in the performance of his usual duties and his conversation and actions will be governed accordingly.

Delusions of persecution are commonly experienced; the patient is suspicious of nurse, physician and attendants; he refuses food for fear it is poisoned. He is apprehensive of all sorts of imaginary dangers, and may as a result attempt to make his escape, preferring, as a rule, the window as an avenue of egress. In other cases the patient may experience terrorizing hallucinations, and become aroused to the highest degree of maniacal excitement. Under the influence of these insane impulses self-destruction may be attempted or aggressive assault may be made upon the attendants.

Cases are on record in which patients have leaped headlong from windows in their suicidal endeavors. The greatest vigilance is necessary on the part of the attendants in the care of patients suffering from this disease.

In severe cases the delirium terminates in coma, which, in fatal cases, becomes progressively more profound. The tongue and hands are tremulous and there is twitching of the muscles and picking at the bed-clothes. When coma-vigil develops the patient is in a most desperate state; the patient neither sees nor hears, although the eyes are wide open and staring fixedly into space.

In rare cases epileptiform convulsions are observed, the patient

lapsing into coma after the subsidence of the convulsive movements. This only occurs in the worst cases and is usually associated with the presence of considerable albumin in the urine.

In cases terminating fatally there is a progressively deepening coma from which the patient cannot be aroused. The patient is, of course, unable to swallow; urine and feces are passed involuntarily; the pulse becomes rapid feeble and intermittent; the respirations are hurried and shallow and death takes place from exhaustion.

Most writers refer to a *disturbance of hearing,* beginning usually toward the end of the first week and amounting in some cases to complete deafness. Curschmann claims that auditory disturbances do not make their appearance until the period of convalescence, when they become comparatively frequent.

He ascribes the deafness not to the action of the toxin on the auditory centers, but to a catarrhal otitis media which at times ends in abscess of the middle ear, with perforation.

Gastro-intestinal Tract.—The tongue in the beginning is covered with a thick, whitish fur; later, it becomes dry and brown. During the comatose state it is commonly hard and leathery and covered with dried blood which issues from the fissures. The mucous membrane of the mouth and lips are likewise dry and covered with sordes.

Thirst and anorexia are common symptoms at the onset of the disease. Vomiting is not common, but occasionally occurs during the period of invasion. In rare cases it may be repeated and accompanied by epigastric pain.

Constipation is the rule in nine-tenths of the cases during the first week. Later in the disease diarrhea may set in and stools may be passed involuntarily. It is associated with meteorism and some abdominal tenderness. Loose movements are believed by many physicians to be due to the liquid diet upon which the patients are kept. The stools do not possess the distinctive character of the typhoid fever dejecta.

Respiratory Tract.—A catarrhal condition of the entire respiratory tract, but especially the bronchial tubes, is so commonly seen in typhus fever as to belong properly to the symptomatology of the disease.

This process involves the naso-pharynx, larynx, trachea and bronchial tubes to their smallest ramifications.

Bronchitis.—Bronchitis is usually present during the first week; the cough is, as a rule, slight and accompanied by little or no expectoration. In the second week the bronchitis may become more widespread, and, through involvement of the terminal bronchioles, lead to atelectasis or bronchopneumonia.

Hypostatic Congestion.—Hypostatic congestion of the lungs is not uncommon owing to the recumbent position in which the patient persistently lies.

Bronchopneumonia.—Bronchopneumonia and lobar pneumonia are common complications and are not infrequently overlooked owing to

the gravity of the more conspicuous symptoms. In addition, pain, cough and expectoration may be slight or absent. Lividity of the face and an increase in respiratory frequency are suspicious symptoms. The lungs should be carefully auscultated from time to time, to discover pneumonia or hypostatic congestion in their incipiency.

Lobular or lobar pneumonia is a frequent cause of death, particularly in some epidemics.

Laryngitis.—Laryngitis is present quite commonly and gives rise to hoarseness and at times aphonia. Ordinarily this is due merely to a catarrhal inflammation of the laryngeal mucous membrane. In severe cases erosions and ulcerations may occur and lead to perichondritis and necrosis of the thyroid cartilage.

Kidneys and Urine.—The urine in typhus fever does not present any characteristics peculiar to the disease. As is the case in other febrile infectious disease the urine is of high color and specific gravity and shows an increase in the amount of urea and other solid organic constituents.

In cases with high fever a moderate febrile albuminuria is observed during the height of the pyrexia. This may be accompanied by the presence of a few hyaline casts.

True parenchymatous nephritis, evidenced by pronounced albuminuria, epithelial and hyaline casts, and at times blood, is fortunately an uncommon complication.

Brill's Disease.—Typhus fever is said to have been introduced into the United States by Irish immigrants after the famine in 1846. Typhus fever was observed in New York in 1850 and 1851. The last epidemic in New York occurred in 1892, when 8 out of 12 doctors in the Bellevue Hospital contracted the disease and died.

In 1910 Brill, of New York, described a disease which subsequently became known as Brill's disease, which he had observed in endemic form in New York since 1896. It had been regarded as typhoid fever but subsequently was demonstrated to be a mild form of typhus fever. Beginning with the usual prodromes, the fever increases rapidly and reaches its height about 103° to 104° F. On the fifth or sixth day a dull red, maculo-papular eruption appears. The rash persists until the crisis and then fades rapidly. The patients are prostrated with severe headache and usually constipation. The fever usually lasts twelve to fifteen days and then declines rapidly by crisis. Convalescence is rapid and fatalities rare. Among 255 cases seen by Brill, the mortality was less than 1 per cent. The disease does not appear to spread to other patients in the ward or home.

Anderson and Goldberger, of the United States Public Health Service, showed by cross-immunity experiments that Brill's disease was identical with Mexican typhus fever. They demonstrated that a monkey inoculated with tabardillo was immune against Brill's disease and *vice versa*. Plotz proved that the organism isolated from cases of Brill's disease and from epidemic typhus was identical.

Endemic typhus has since been reported in many states, including New York, Massachusetts, Pennsylvania, Maryland, Georgia, Indiana, Minnesota and California.

According to Netter and Blaizot, an attenuated endemic form of typhus similar to Brill's disease has existed for some time in Paris.

COMPLICATIONS AND SEQUELÆ OF TYPHUS FEVER.

In addition to bronchopneumonia, nephritis, otitis media, etc., which were referred to under the head of symptomatology, there are other complications which occur from time to time during the course of typhus fever.

Bed-sores.—Bed-sores are not infrequently observed in dependent areas subjected to pressure. Curschmann found this complication present in about 3 per cent of his cases. The supine position constantly maintained by typhus patients favors the development of a necrosis of the skin over the back, particularly in the region of the sacrum.

Gangrene.—Gangrene of the skin, particularly of terminal members, such as the toes, ears and fingers has been noted by a large number of physicians. When gangrene of the lower extremities develops there are pain and numbness in the limbs, followed by a lowering of the temperature of the affected parts. The pulsations in the arteries cease and the toes begin to exhibit a livid hue, which later becomes purplish and finally black. The skin and subjacent tissues become hard and dry and mummification sets in. A line of demarcation may form and spontaneous amputation result, or surgical removal may become necessary. In some cases the sphacelation may take the form of a moist gangrene.

The terminal gangrene above referred to is doubtless due to an arteritis with the formation of arterial thrombi. When the veins of the legs are attacked, with the production of a phlebitis, the affected members become hot and swollen and take on the ordinary appearance a *phlegmasia alba dolens*.

Noma.—Noma, or cancrum oris, occasionally develops in the course of typhus fever, as it does in some other exanthemata.

Erysipelas.—Erysipelas is a complication much spoken of by the older writers, but it is much less common at the present day owing to the better hygienic conditions which prevail in modern hospitals.

Boils.—Boils and subcutaneous abscesses are met with more frequently in some epidemics of typhus than in others. They develop, as a rule, during the convalescent stage, which may be as a result thereof prolonged.

Parotitis.—Parotitis appears to be one of the most frequent complications of typhus. It is encountered with unusual frequency in certain epidemics. Schilling, of New York, in 1852, observed it in about 20 per cent of his cases. This, to be sure, is an unusually high

incidence. The inflammation may come on at any stage of the disease, but most commonly during the third week. One or both sides may be affected. In the majority of cases the inflamed gland goes on to suppuration. In some cases the submaxillary salivary glands enlarge and undergo abscess formation. These abscesses add considerably to the gravity of the disease.

Jaundice.—Mild attacks of jaundice are not rare in the course of typhus fever; in some epidemics the icterus has been so intense as to suggest the existence of some other disease with hepatic disturbance.

Other Complications.—Local or general paralysis, gangrene of the lungs and suppuration of the joints might also be mentioned as among the rare complications of typhus fever.

Temporary Insanity.—Temporarily insanity in one of its various forms has been known to persist for some time after convalescence from typhus. Roupell mentions the case of a woman, aged twenty-two years, who suffered from mania and who was confined in a lunatic asylum for several months after convalescence from the disease, ultimately making a complete recovery from the mental aberration.

Duration of the Disease and Variations in the Course.—The majority of writers are in accord that the duration of typhus fever under ordinary circumstances is about fourteen days. It is not rare for the disease to run a course of one or two days longer than this period, or, on the other hand, to terminate a day or two before the fortnight is completed.

It is uncommon for the fever to persist in uncomplicated cases after the eighteenth day and distinctly rare after the end of three weeks. Lebert says that he has exceptionally seen "the duration of the disease prolonged to five or six weeks, not merely by complications, but also by protracted convalescence of a slight febrile character."

Curschmann has observed cases beginning with marked *hyperpyrexia* run an unusually protracted course to a fatal termination. Under such circumstances, the fever, very high in the beginning, may fall to normal or below, where it may continue for some days or a week before death takes place. A fatal termination may be delayed to the end of the second or the middle of the third week.

Various authors have described cases of typhus of unusual *malignancy* which terminated fatally in a few days; this form of the disease was designated *typhus siderans* by the older writers. The symptoms, in brief, are a severe chill, rapid rise of temperature to great height, repeated vomiting, severe cephalalgia and general pains, frequent small pulse and rapid clouding of the mental faculties. The spleen is found to be distinctly enlarged in these cases. The eruption is wholly or in part suppressed. Death may supervene in the course of two or three days, and in rare cases, it is said, within a day or two after the onset of the disease.

Hemorrhagic Typhus Fever.—Hemorrhagic typhus fever is an excessively rare variety. The invasive symptoms are of great severity

and are followed about the third day by hemorrhagic extravasation into the skin in the form of petechiæ and larger ecchymoses. In addition, hemorrhages occur into the conjunctivæ and from the various mucous surfaces—from the mouth, nose, kidneys, uterus, intestines, etc.

There is pronounced cardiac weakness, profound prostration and, in some cases, gangrenous complications. These cases exhibit a striking parallelism with that form of hemorrhagic smallpox known as purpura variolosa.

Under the heading of *abortive cases* of typhus fever, Curschmann describes attacks characterized by a violent chill followed by a rise in temperature, which reaches its maximum in twenty-four to thirty-six hours. For several days the pyrexia persists as a continued or continued remittent fever, then declining rapidly by crisis to the normal line, where it remains. In these cases the fever may have run its course by the fifth or sixth day or earlier. The accompanying symptoms may be severe and alarming, even after the temperature begins to fall.

The rash in these cases is usually scanty and of short duration. In those cases in which it is absent the diagnosis may be rendered extremely difficult and at times impossible.

Writers have referred to different varieties of typhus fever under such names as *inflammatory* typhus, *ataxic* typhus, *adynamic* typhus, etc. These designations and many others have been used to classify certain expressions of the disease, but as they tend rather to complicate than to clear one's comprehension of typhus they might well be permitted to become obsolete.

THE DIAGNOSIS OF TYPHUS FEVER.

Although there is no pathognomonic symptom which distinguishes typhus fever from other diseases, yet the symptom-complex is sufficiently distinctive and well defined to render the diagnosis clear in the vast majority of cases.

The mode of onset, the rapid rise of fever to its maximum, the early development of pronounced cerebral symptoms, the peculiar facies, the characteristic rash and the nature of the pyrexial curve collectively bespeak a disease which can be trenchantly separated from all other infectious maladies.

Typhoid Fever.—It is only within the last half-century that typhus has been clearly distinguished from typhoid or enteric fever. Exceptionally, individual cases still arise in which the differential diagnosis is difficult, but under ordinary circumstances these two diseases should not be confounded.

Typhus and typhoid fever prevail under different conditions, and spread in a different manner. The former is endemic in certain countries, but may reach other localities during epidemic prevalence of the disease. It is distinctly contagious and becomes disseminated through

the contact of the well with the sick or through the intermediation of infected articles. Typhoid fever spreads in several ways, but chiefly through a contaminated water supply; it is not contagious, at least according to the usual acceptation of this term.

An attack of typhoid fever is usually preceded by a period of indisposition and *malaise*. Typhus fever in the majority of cases is ushered in suddenly and without prodromal illness.

The pyrexial curve varies considerably in the two diseases. In typhoid fever there is a step-like ascent for about a week, then about a week of even temperature, and finally a gradual decline occupying about the same period. The fever in typhus rises more rapidly, reaches its maximum about the fourth or fifth day and declines to normal by a more or less critical fall about the end of the second week. The morning remissions are less pronounced than in typhoid, and the febrile course is, with rare exceptions, distinctly less protracted.

The pulse of typhoid fever is in general slower and more often exhibits dicrotism than the pulse of typhus.

The chill, headache, pains in the legs and prostration are all more intense in typhus. The nervous symptoms come on at an earlier date and the psychic disturbance, particularly the delirium, is more violent. The flushed and edematous face, injected conjunctivæ and general wild expression of typhus patients contrasts strongly with the pale, depressed countenance of typhoid patients.

The eruption of typhus develops earlier (about the fifth day), comes out in one continuous crop and is usually more profuse than that of typhoid fever. It must be remembered, however, that the typhoid exanthem may occasionally be abundant and the typhus eruption sparse.

The rash of typhoid is generally limited to the trunk, whereas the typhus spots involve the trunk and extremities, even to the hands and feet. The typhoid spots come out in separate crops and are more papular and have a more defined border than typhus lesions. The latter, moreover, tend to become petechial, when they no longer disappear under pressure as do the typhoid rose spots.

Typhoid fever is more often accompanied by meteorism, gurgling the right iliac fossa, diarrhea and the peculiar pea-soup stools.

The mean duration of typhoid fever is three weeks and of typhus two weeks. In addition to the above clinical symptoms, certain tests are of importance. The agglutination reaction of Widal will aid in the diagnosis of typhoid fever, but not during the early days. Eberth's bacilli may be recovered from the spleen, or from the urine, stools, blood or rose spots. On autopsy Peyer's patches will be found to be ulcerated in typhoid fever, but not in typhus.

Relapsing Fever.—The differentiation of typhus and relapsing fever may be attended with great difficulty, particularly during the onset of the disease. In both maladies the fever rises rapidly to great height. Typhus, however, is accompanied by much more severe constitutional

commotion and by greater mental disturbance; in relapsing fever the mind remains clear and the general condition remarkably good. Furthermore, there is entire absence of a cutaneous eruption. At the end of five or seven days in relapsing fever the temperature subsides to normal, where it remains for a similar period, then rising and ushering in the relapse. Jaundice is observed in a large number of cases. Examination of the blood will reveal the presence of the spirillum of Obermeier.

Malarial Fever.—In tropical countries and even elsewhere at times, a malignant form of remittent fever is seen which may in some respects closely resemble typhus fever. The high fever is accompanied by great prostration and early disorder of the mental faculties. Later, manifestations of the typhoid state may make their appearance. Where doubt exists the examination of the blood will reveal the presence of the hematozoa of malaria and the diagnosis will thus be rendered clear.

Meningitis.—Both in idiopathic meningitis and in the epidemic variety a similarity to typhus fever may be presented through the predominance of the cerebral symptoms. Cerebrospinal meningitis is, moreover, accompanied by an eruption which may lead to error. It is only, however, when the symptomatology is irregular that real difficulties in the diagnosis are presented. In meningitis the headache is more intense and of a sharp, boring character. Nausea and vomiting, which are rare symptoms in typhus, are apt to be present. Rigidity of the muscles of the neck and retraction of the head are of great diagnostic importance in meningitis. Later various paralyses develop.

Pneumonia.—In certain forms of pneumonia attended with typhoidal manifestations and masked pulmonary symptoms there may be a resemblance to typhus fever. The rash will be absent and a careful examination of the chest will discover the presence of consolidation of the lung.

Delirium Tremens.—Typhus fever occurring in persons strongly habituated to the use of intoxicating liquors may present symptoms simulating *mania a potu*. Insomnia, delirium and muscular tremblings may be present in both conditions. The high fever, eruption and course of the disease will readily distinguish typhus fever.

In the eruptive stage typhus fever may be confounded with measles, with hemorrhagic smallpox, and with severe forms of purpura.

Measles.—During the evolution of the eruption, the typhus exantham, particularly when it is profuse, with a tendency to coalesce, may closely simulate that of measles. This is especially true in the case of children, in whom it may occasionally appear upon the face. Roupell believes that Sydenham was probably dealing with an epidemic of typhus fever in 1674, when he described an anomalous and malignant form of measles. Sydenham[1] says: "The measles of 1674 deviated

[1] Opera, p. 232.

from rule, did not preserve their type; the eruption came out irregularly, was often confined to the neck and shoulders. The bran-like desquamation did not result, peripneumonia more frequently took place, and in some cases the fever would last fourteen days or more.

Typhus differs from measles in many particulars, and may usually be readily differentiated. The prodromal stage of measles is characterized by marked catarrhal symptoms giving rise to sneezing and coughing; the fever rises gradually and not to such a height as in typhus; the face is profusely covered with the rash, which spreads downward over the trunk and extremities. In typhus the fever soon reaches its maximum and the febrile course is longer. The rash seldom occurs on the face, the rose spots later exhibit petechial change and the sensorium is more profoundly affected; patients previously attacked by measles are susceptible to the disease.

Smallpox.—The symptoms of the initial stage of smallpox and typhus fever present a striking similarity. In each disease we have chills, sudden high fever, headache, general pains and profound prostration. Vomiting is much more frequent in variola than in typhus. The appearance of the characteristic eruption on the third day after the onset of the fever in variola will clear up the diagnosis. Between purpura variolosa and hemorrhagic typhus fever a differentiation is often impossible. Both are characterized by hemorrhages into the skin and from the various mucous membranes, associated with intense prostration and death in a few days. The knowledge of the prevalence of one or the other disease will aid in the diagnosis.

Purpura.—Severe cases of purpura hæmorrhagica may likewise be confounded with malignant typhus fever. The former, however, is seldom ushered in with intense fever and the prostration in the beginning is not extreme. It is only under exceptional circumstances that a confusion of the two diseases would take place.

THE PROGNOSIS OF TYPHUS FEVER.

The wide divergence in the mortality-rates of epidemics of typhus fever many years ago is doubtless due to the fact that typhoid fever, relapsing fever and typhus fever are often confounded and considered one and the same disease.

The fatality of typhus is influenced by many factors, chief among which are the age of the patient, his hygienic environment, the condition of his health prior to the attack and the severity of the prevailing type of the disease. These and other influences will be considered in detail.

Age.—The age of the patient influences the mortality to a considerable extent. With the exception of very young children the disease is much less fatal in childhood and youth than in age periods beyond these. Beyond the age of twenty years the mortality progressively increases, reaching its maximum in advanced old age. Below are

appended three series of age statistics. In the town of Greenock, according to Buchanan, the death-rate was as follows:

Age.	Mortality, per cent.
Under 12 years	5.0
10 to 20 "	8.6
20 to 30 "	15.6
30 to 40 "	21.5
40 to 50 "	42.0
Over 50 "	66.6

The death-rates of typhus fever in the London Fever Hospital, during a period of two years and including 3506 cases, have been calculated by Murchison as follows:

Age.	Admitted.	Died.	Per cent.
Under 5 years	17	3	17.65
Between 5 and 10 "	183	14	7.65
10 and 15 "	363	18	4.95
15 and 20 "	546	26	4.76
20 and 25 "	495	47	9.05
25 and 30 "	343	52	15.15
30 and 35 "	323	55	17.02
35 and 40 "	270	89	32.96
40 and 45 "	292	87	29.79
45 and 50 "	212	83	39.15
50 and 55 "	150	78	52.00
55 and 60 "	100	51	51.00
60 and 65 "	88	49	55.68
65 and 70 "	42	28	66.66
70 and 75 "	24	17	70.83
75 and 80 "	6	5	83.33
Over 80 "	2	2	100.00
Age unknown	50	11	22.00
	3506	715	20.39

Guttstadt[1] gives the figures for 5545 cases admitted into Prussian hospitals from 1878 to 1880:

Age.	Males, per cent.	Females, per cent.
Under 10 years	2.2	3.3
Between 10 and 15 "	3.0	1.5
15 and 20 "	5.2	4.5
20 and 30 "	8.2	10.1
30 and 40 "	16.0	11.2
40 and 50 "	31.9	20.2
50 and 60 "	43.7	35.5
Over 60 "	57.1	45.2

It will be seen that while Guttstadt's tables exhibit lower mortality-rates than Murchison's, the same general influence of age is shown.

Curschmann believes that the increasing death-rate after the age of forty years is due to the great cardiac weakness at this period and to the increased liability to hypostatic congestion of the lungs and other pulmonary complications as a result thereof.

[1] Quoted by Curschmann.

Sex.—Sex appears to exert but little influence upon mortality. Murchison's figures give 19.67 per cent of deaths in males and 18.2 per cent in females.

Hygienic Environment.—The social position and financial condition of individuals influence to a large extent the character of their surroundings. Food, mode of life and domiciliary environment, by modifying the physical, mental and moral tone of persons, influence to that extent their general health and resistance to disease, and also their ability to successfully cope with disease when stricken.

The mortality of typhus fever is particularly high among people debilitated by famine and hardship. Physical exhaustion, such as occurs in soldiers and among hard-worked nurses and physicians, doubtless accounts for the comparatively high mortalities among these classes of patients. The overcrowding and unhygienic conditions which often prevail in barracks, prisons and on board ships increase not only the incidence of typhus but also its mortality.

Murchison divided the patients admitted into the London Fever Hospital into three classes, according to their social and financial condition:

	Admitted.	Died.	Per cent.
Pay patients	95	15	14.89
Patients admitted free, but not classified as paupers	2674	497	18.60
Paupers	738	204	27.60

It is seen from these figures that the mortality is higher according to the poverty of the patients. Murchison believes, however, that the larger death-rate among the poorer patients is to be explained by the more advanced age of these persons. He states that the current opinion in Ireland is that the disease is accompanied by a higher mortality among the rich than among the poor.

Intemperance and Previous Health of Patient.—It is no less true of typhus fever than of smallpox and other infections that the disease is particularly fatal to alcoholics. Prolonged habits of intemperance produce structural changes in the heart, bloodvessels, kidneys, liver and nervous system, and weaken the defensive resources of the body when attacked by disease. In typhus fever, as in smallpox, hemorrhagic attacks are more common in drunkards than in other individuals.

The previous existence of chronic organic diseases or of acute diseases unfavorably influences the prognosis in typhus fever, as would naturally be expected. Debilitating illnesses which lower the resisting power of the individual, or diseases in which the structural integrity of important organs is affected, very considerably lessen the chances of recovery.

Unfavorable Symptoms.—Great intensity of any or all of the symptoms of typhus fever constitutes an unfavorable condition, yet the comparatively brief course of the disease renders it possible for patients exhibiting even the most alarming symptoms to recover.

High fever during the invasive stage and the remaining days of the disease, if unattended by symptoms hereafter to be mentioned, need not be regarded as of specially unfavorable significance. If, however, the temperature continues very high during the second week it indicates an attack of great gravity.

More important than the temperature is the condition of the heart and the bloodvessels. Licéaga regards an early disproportion between the pulse-rate and the temperature as a sign of fatal omen. A pulse-rate of over 120 in the beginning of typhus fever should excite solicitude. But the frequency of the pulse is not the only factor to be considered. The rhythm, volume and compressibility of the arterial pulsations and the character of the cardiac sounds are of equal or greater importance. Inaudibility of the first heart sound or irregularity, rapidity or marked compressibility of the pulse occurring early in the disease are bad prognostic signs.

The condition of the nervous system offers valuable evidence. Early wild delirium, persistent insomnia, progressively deepening stupor, subsultus tendinum, carphologia, muscular twitchings and convulsions are all of evil portent. The occurrence of profound coma or coma-vigil renders the prognosis hopeless.

The presence of considerable albumin in the urine during the early days of the disease indicates a grave infection. When blood and casts are associated an alarming complication is present.

Pulmonary complications are commonly the cause of death, particularly in persons advanced in years. Hypostatic congestion, severe and widespread bronchitis and pneumonia swell the mortality list. Curschmann includes marked meteorism and "pin-hole pupils" among the specially unfavorable symptoms.

The profusion of the rash is of less prognostic import than its special characters. The early appearance of petechiæ and an unusual degree of hemorrhagic extravasation into the skin are grave signs. Pronounced cyanosis of the skin, particularly of the face and extremities, indicates cardiac weakness and is, therefore, an ominous manifestation.

Among the *favorable* symptoms are moderate intensity of the fever, ability to sleep, preservation of the faculties of the mind, moist tongue, moderate frequency of the cardiac pulsations and early subsidence of the pyrexia.

Mortality-rate.—The death-rate of typhus fever varies considerably in different epidemics, but will be found usually to be in the neighborhood of 18 or 20 per cent. Murchison found that the mortality of 4787 cases of typhus fever treated in the London Fever Hospital between 1848 and 1862 amounted to 20.89 per cent. The same author collected the immense number of 18,592 cases treated in London, Glasgow and other cities, and calculated the mortality as 18.78 per cent. Lebert gives the general mortality in his experience as 15 per cent; Buchanan, 10 per cent; Curschmann, 23.4 per cent.

The mortality in hospitals is higher than in private practice. This

may be in part accounted for by the larger percentage of grave and moribund cases received in hospitals.

In the most severe epidemics the mortality may reach 30, 40 or even 50 per cent. During military campaigns and in famine-stricken communities the death-rate is apt to be particularly high.

THE TREATMENT OF TYPHUS FEVER.

Prophylaxis.—The question of prophylaxis concerns itself with the handling of those exposed to typhus fever and those suffering from it. Great strides have been made since the mode of transmission by the louse has been demonstrated. The problem is really the prevention of vermin infestation. Ninety per cent of the American troops in the World War were infested with vermin.

Head lice are most rapidly destroyed by anointing the head with equal parts of kerosene and olive oil or kerosene and vinegar and wrapping a towel around the head overnight. This should be followed by shampoos and combing with a fine comb. In males the hair should be clipped. For the destruction of lice in clothing steam disinfection is best. Where this is not possible they should be subjected to sulphur (not formaldehyde) fumigation in a closed receptacle, such as a trunk.

Lice and nits are destroyed at a dry heat temperature of 55° C. (131° F.) for five minutes. It is, however, better to heat to 70° C. (135° F.) for thirty minutes. Steam disinfection should be continued for twenty to thirty minutes.

Insecticide powders have not given particularly satisfactory results in preventing infestation. The English used with some success a powder made up of commercial naphthalene, 96 per cent, creosote, 2 per cent, and iodoform, 2 per cent. The powder acts as a repellent, but does not destroy nits. It should be dusted into the seams of the clothing every three days.

The room from which a typhus patient is removed should be fumigated with hydrocyanic acid gas, 3 to 3½ ounces (90 to 105 cc.) per 100 cubic feet, with 25-inch vacuum for two hours. The gas is very poisonous.

In the field physicians should wear a combination undersuit of closely woven white cotton. This garment should be worn under or just over the undergarments. There should be long sleeves tied about the wrists. Rubber boots or high laced shoes should be worn to prevent the louse from crawling up from the floor.

Woolens should be avoided because of the clinging surface.

At the end of the day's work the outer garment which consists of a long surgeon's gown should be hung up where it will not come in contact with other clothing. A bath should be taken at night and the body then sponged with a soapy water made of germicidal soap which should not be washed off.

Typhus is said not to be as frequently conveyed by the bite of the

louse as it is from the crushing of the louse and smearing the débris over an abraded skin surface. When one feels the bite of a louse instead of crushing it one should pour chloroform over the area through the clothes. Chloroform appears to neutralize the virus of the louse.

The following method of delousing patients is advised:[1]

All the hair is clipped from the head, arm pits, body and pubis, and the patient is thoroughly scrubbed with soap and running hot water. Then the hairy parts are wetted with kerosene (coal oil). Clean pajamas are then donned, he is wrapped in a clean blanket and transferred to his bed in the hospital. The clothes are subjected to high-pressure steam sterilization.

Physicians and nurses should not handle louse-infested patients if typhus immunes are present to do this work.

All contacts should be isolated fourteen days in a separate building and be carefully deloused before admission.

Experience has shown that the control of vermin infestation lowers the incidence of the disease. Nicolle and Conseil working in Tunis, on the eradication of the louse, achieved the results set forth below:

Year.	Cases.
1909	856
1910	148
1911	180
1912	22
1913	6
1914	3
1915	0

Isolation.—As is true of all contagious diseases, the typhus patient must be separated from other persons during the entire period of his illness. This can be most effectively accomplished by sending him to a hospital especially set apart for the purpose. No one at the present day would hazard placing a typhus patient in the wards of a general hospital.

Where the patient must be treated at his home an airy and well-ventilated room in the upper part of the house should be selected.

Carpets, curtains and all dispensable furniture should be removed from the apartment. A communicating room should be occupied by the nurse and likewise utilized to disinfect all articles leaving the sick-apartment. Over the door communicating with the corridor should be suspended a sheet wet with a 5 per cent solution of carbolic acid or a 1 to 1000 solution of bichloride of mercury. Whenever possible the attendants and nurses should be chosen from those who have once passed through an attack of the disease. One attack of typhus fever protects against a second in the vast majority of cases. When an immune nurse cannot be secured the one employed had better not sleep in the sick-room. Non-immune nurses should not be permitted to go abroad among people, for fear of spreading the disease.

[1] From letter of Dr. J. R. Ranson, American Sanitary Red Cross Inspector, Salonika, Greece, Jour. Am. Med. Assn., 1921, **77**, 1120.

Disinfection.—The destruction of the infection in all articles with which the patient has come in contact is a measure of the highest importance. Mention has already been made of the frequent transmission of typhus fever in the body linen of patients. To lessen the intensity of the infection in these articles frequent bathing of typhus patients is desirable. The baths, which may be sponge or plunge baths, subserve the double purpose of reducing temperature and lessening the dissmination of the contagium of the disease.

The body and bed linen should be changed once or twice a day. They should be boiled.

The physician in attendance upon typhus patients should protect his clothing by wearing a long gown and cap which covers as much of his hair as possible. On leaving the patient he should carefully wash his face and hands and change all of his clothes.

After the recovery of the typhus patient the apartments occupied should be thoroughly fumigated with sulphur or hydrocyanic acid gas. Walls should be whitewashed, painted or repapered according to desire. Blankets and mattresses should be subjected to superheated steam or hot air in the disinfecting plant provided by most large cities. When such facilities are not available blankets should be boiled and mattresses burned and destroyed.

Wooden furniture should be washed with a solution of carbolic acid or bichloride of mercury. The patients' clothing should be disinfected by steam or hot air.

When death occurs the body should be enveloped in a sheet saturated with a carbolic acid or corrosive sublimate solution. An hermetically sealed casket should be used and interment should be private.

Nursing.—The nursing of typhus fever is of great importance and requires the services of a trained person. The body surface should be frequently sponged with water containing a little alcohol or with a weak carbolized solution. The teeth and oral cavity require careful attention from the beginning; mild antiseptic mouth washes should be employed. Diluted Dobell's solution, boric acid water or a diluted peroxide of hydrogen may be used. The cleansing of the mouth is of particular importance when the patient is stuporous, as the mucous membrane becomes dry and covered with mucus and blood crusts.

Careful attention is necessary to prevent the development of bedsores. Frequent ablutions of parts subjected to pressure and soiled by excretions, and the use of pads or pneumatic cushions to relieve pressure, will accomplish the object desired.

Diet.—The diet is the same as that prescribed in the other acute exanthemata. During the intense febrile period the patient will desire nothing but liquid nourishment. Milk and broths may be given every two or three hours. As soon as the patient care for soft foods he may be allowed to have soft-boiled eggs, gelatin, gruels, milk-toast and like foods. As the disease abates and the appetite increases, a gradual return to the usual dietary may be begun. For the relief of thirst

lemonade and the carbonated waters may be given. The diet need not be as rigid as in typhoid fever, in which disease the presence of intestinal ulceration necessitates great caution.

Medical Treatment.—Although numerous remedies have been advocated from time to time for their beneficial action upon typhus fever, it must be admitted that we know of no drug which materially affects the course of the disease. When the specific cause of typhus is discovered a specific cure for the disease may be forthcoming. The most approved treatment of typhus is that which is devoted to an alleviation of the symptoms and the maintenance of the patient's strength.

Brenner[1] states that the most useful measures in typhus fever are an abundance of fresh air and keeping the patient under the influence of *turpentine*. He gave in 150 cases from 0.05 to 0.1 gm. at hour intervals and used during the night pledgets of cotton soaked in turpentine in the nostrils. When begun not later than the third to the fifth day it is alleged to have abbreviated the course of the disease materially and to have brought about improvement in virtually all cases.

Dianderas[2] treated 25 cases of typhus and all recovered. He gave in addition to the usual treatment subcutaneous injections of turpentine (1 cc. in a mixture of 10 cc. of alcohol at 40° C. and 10 cc. of turpentine; 4 cc. of a 0.5 per cent solution of sodium chloride). He ascribes a specific efficacy to the turpentine, in addition to the fixation abscess effect.

The prophylactic use of intravenous injections of convalescent serum has been employed on a small scale by Nicolle and Conseil with satisfactory results. It has also been employed during the course of the disease.

Intravenous injections of urotropin have been used by Glatard in doses of 1.5 gm. for adults and one-half of this dose for children. Defervescence of the temperature is said to commonly occur after the second injection. The mortality was 14 per cent as against 29 per cent in patients not treated by this method.

Fever.—The fever in typhus often reaches a great height and calls for measures to reduce its intensity. Almost exclusive reliance is to be placed upon hydrotherapy in one form or another. In the milder cases it may suffice to employ tepid sponge baths several times a day. The application of an ice-bag or Leiter's coil to the head is a useful supplementary measure. When sponge baths are not sufficient to control the pyrexia recourse may be had to the wet pack, the sheet being wrung out of tepid or cold water, according to the intensity of the fever. The continuous tepid or warm bath will be found to control the temperature in a most satisfactory manner; the patient may be kept for twenty-four hours or longer in a bath, the temperature of which is maintained between 93° and 98° F. When the graduated bath

[1] Med. Klin., 1921, **17**, 992.
[2] Cronicá méd., Lima, 1924, **41**, 229.

is employed the water is at first warm, but is gradually lowered by the addition of cold water to 75° or 70° F.

The Brand method of cold bathing formerly so extensively used in the treatment of typhoid fever does not seem to have been systematically tried in typhus fever, although its main features are referred to in favorable terms by those experienced in the treatment of typhus. With one or other of the above hydrotherapeutic measures it will be found possible to control excessive fever. It should be remembered that the reduction of fever by these measures is merely one of the objects desired. Baths exert a tonic influence upon the respiratory and circulatory centers and allay nervous excitability.

The coal-tar antipyretics should not be used except in very moderate doses. When given in large doses or over a long period of time they may produce serious cardiac depression. Phenacetin, antipyrin and lactophenin are among the most eligible of these preparations.

Nervous Symptoms.— *Headache* is commonly so persistent and distressing as to require remedies for relief. The light in the room should be kept subdued in order to lessen retinal irritation. An ice-bag should be applied to the head, and bromide of sodium, phenacetin or antipyrin administered. When these remedies fail to control the cephalgia it may be necessary to give opium.

Insomnia.—Inability to sleep is a bitter complaint of typhus patients during the early days of the disease. It is well to first try the bromide of sodium in 20-gr. doses, repeated once or twice during the night.

In other cases chloral appears to do well, but should not be used in large doses for fear of depressing the heart. Ten grains may be administered in the evening, and followed later by a 15-gr. dose if necessary. Where sleep cannot be otherwise obtained it is proper to give a hypodermic injection of morphine. The employment of a warm or tepid bath at the sleeping hour will often materially aid in quieting nervous excitement and inducing sleep.

Delirium.—The bromides, chloral and opium may be employed to quiet excessive cerebral activity. The best result in many cases is obtained by an ice-bag to the head and a prolonged warm bath, or, when the temperature is very high, a cold bath or pack.

Constipation.—In the constipation which usually exists early in the disease calomel in fractional doses may be given or a mild saline may be used. One of the disadvantages of employing opium in typhus is the aggravation of the existing constipation. When there is much fever a cold, high enema will serve a double purpose. Vomiting, when present, may be controlled by pellets of ice, carbonated or lime water and temporary abstention from food. The late diarrhea is best checked by bismuth internally, and starch water and laudanum enemata. Meteorism may, when mild, be relieved by laxatives and turpentine internally and externally. Severe gaseous distention occurring late is a grave symptom, often defying all treatment.

Alcohol.—Alcohol is a remedy of great value in the treatment of typhus, when it is used with discrimination. It should not be employed as a routine, but rather to combat special symptoms. Many patients will not require its use at all. Buchanan says that alcohol is needed in two classes of patients—those who cannot take a sufficient quantity of nourishment and those habituated to the use of stimulants. He enumerates the special indications as follows: Alcoholic stimulants are most serviceable in (1) old people; (2) in cases of great prostration with low delirium and coma; (3) where the pulse is very compressible, the first heart sound feeble and also when the pulse is rapid or irregular; (4) where the extremities are cold and the surface livid; (5) where there is much congestion of the lung; (6) where there is any erysipelatous complication.

It may be given in the form of whiskey, brandy, or wine, or, as Curschmann prefers, in Stokes' cognac mixture, the formula of which is as follows:

℞—Cognac opt.,
Aquæ dest. . . . . āā ℥15
Vitelli ovi . . . . . No. 1
Syrupi . . . . . ℥6
Sig.—Tablespoonful every two or three hours.

When the *pulse* becomes compressible, rapid or irregular, or when the first heart sound is weak, it may be necessary to resort to other cardiac stimulants in addition to alcohol. Strychnine, digitalis, strophanthus and caffeine may be employed with advantage. Nitroglycerin and camphor dissolved in olive oil may be used hypodermically to tide over critical moments.

Pulmonary and renal complications are to be treated in the same manner as when these conditions arise independently.

Serum and Non-specific Protein Treatment.—Nicolle and Blaizot[1] have immunized horses with injections of extracts of suprarenal glands and spleens of guinea-pigs dying of typhus fever. They report that the treatment of 36 cases by subcutaneous injection of this serum in dose of 10 to 20 cc. per day resulted in more prompt defervescence, relief of delirium, stupor and prostration, and that but 1 case died.

Gyori[2] has used auto-serum treatment with benefit in some cases; Munk[3] has employed injections of normal horse serum, peptone and nucleohexyl.

During the World War a number of these non-specific agents were employed. Holler[4] used daily intravenous injections of deutero-albumose with good results when treatment was begun within two days of the onset. In a series of 50 cases the mortality was 6 per cent, whereas of 15 untreated cases the mortality was about 50 per cent.

[1] Bull. de la Acad. de méd., 1916, **76**, 95.
[2] Deutsch. med. Wchnschr., 1918, **44**, 677.
[3] München. med. Wchnschr., 1916, **63**, 1239.
[4] Med. Klin., 1927, **13**, 1038.

Tagle[1] has used intravenous injections of 4 to 10 cc. of 10 per cent solutions of peptone with a mortality of 5 per cent in 59 cases; children received 4 or 5 cc. Second injections were given about forty-eight hours later, and in some cases a third injection. Opazo[2] has also employed injections of peptone.

Schultz and his colleagues[3] and Kalberlah[4] have employed intravenous injections of typhoid vaccine; especially good results have been reported by Danielopolu[5] with daily intravenous injections of hypotonic salt solution (0.065 per cent).

In conclusion a word of caution should be uttered concerning the necessity for constant vigilance on the part of the nurses and attendants to prevent suicidal or homicidal attempts during maniacal excitement.

[1] Rev. méd. de Chile, 1919, **47**, 413.
[2] Ibid., 433.
[3] Berl. klin. Wchnschr., 1919, **45**, 1226.
[4] Therap. Monatschr., 1918, **32**, 328.
[5] Le typhus exanthematique, Bucharest, 1919.

CHAPTER XIV.

DIPHTHERIA.

Definition.—Diphtheria is an acute infectious disease characterized by the production of a fibrinous exudate or false membrane on certain parts of the mucous surface of the body. The regions by far most commonly involved are the tonsils, the pillars of the fauces, the soft palate, the uvula, the pharynx and the nares. Not infrequently the disease extends into the larynx; or it may begin there primarily and remain limited to this locality. Except at the onset, or when there is laryngeal involvement, febrile reaction is not a prominent symptom.

The disease is caused by a specific microörganism and begins as a local affection, but becomes systemic as the result of absorption of toxins elaborated by the specific bacilli and, perhaps, certain associated bacteria. In severe cases the toxemia may be extreme. After the general symptoms have disappeared paralysis is liable to follow. This may be limited to a few muscles or there may be complete ataxia.

History.—Of the various diseases belonging to the infectious group, which have prevailed from time to time in epidemic form, diphtheria is believed to be one of the oldest. Some writers have sought to prove that it was known at the time of Hippocrates, and described under the name of Malum Ægyptiacum. While in the absence of sufficient literature on the subject this cannot be determined definitely, yet it is true that Aretæus, a Greek physician of Cappadocia, who lived in the latter part of the first and the beginning of the second century, portrayed the critical features of this malady in language which warrants the belief that the disease he described was diphtheria.

In the sixteenth, seventeenth and eighteenth centuries epidemics of a disease presenting the essential characteristics of diphtheria are said to have prevailed frequently, and often with great virulence in many parts of Europe, particularly in Holland, Spain, Italy, France and Germany. The affection appeared also in England, and was described by Fothergill, Huxham and others.

It is not known exactly when this malady made its appearance in America. In 1771 Samuel Bard, of New York, published a brochure entitled, "An Enquiry into the Nature, Cause and Cure of the Angina Suffocativa, or Sore Throat Distemper, as it is Commonly Called by the Inhabitants of this City and Colony." In this article a clinical description is given of a disease comparable in its essential features to diphthera. It prevailed chiefly among children under ten years of age, and was evidently infectious.

After Bard's description of the disease, in 1771, very little seems to

have been said about its presence in New York until 1826. From 1855 to 1858 it prevailed in some part of the state, especially in Albany, with great malignancy.

In 1856 Dr. J. V. Fourgeand published a monograph on a terrible epidemic of sore throat which occurred in San Francisco and other towns of California.

An epidemic of a similar affection occurred in Philadelphia as early as 1809. Again in 1831 another epidemic prevailed. The records of the Health Office of Philadelphia, however, do not show that any deaths occurred in this city from "diphtheria" until 1860, during which year the number reached 307.

The earliest accurate observations on the clinical manifestations of diphtheria were made by Bretonneau, of Tours, in 1821, when he presented his first celebrated paper on the subject to the French Academie de Médecine. This paper, it is said, was not published until 1826. The name he suggested for the disease was *Le Diphthérite*, or Diphtheritis. He gave it this name because of its essential characteristic, namely, the formation of a false membrane. Subsequently the name Diphtheria was proposed by Trousseau.

Trousseau, with his acute power of clinical observation, directed attention to the difference between diphtheria and some of the throat affections, especially scarlatina, with which it was often confounded, and also pointed out the danger of this disease from its liability to extend into the air passages. The fact that death not infrequently resulted at an early period of the disease from an adynamic condition was observed by him and especially commented upon. He is credited with rendering valuable assistance to Bretonneau in establishing the operation of tracheotomy for the relief of membranous croup; even the indications given by him for its adoption would still serve as a useful guide for us at the present day.

Bouchut was the first to practise "tubage" of the larynx for relief of the stenosis caused by membranous croup.

This procedure, however, was condemned and fell into disuse for nearly a quarter of a century, when, in 1880, it was revived and brought to a high state of perfection by O'Dwyer, of New York. Intubation is now almost universally regarded as an indispensable auxiliary in the treatment of membranous croup.

After Bretonneau's publication appeared diphtheria was recognized and described by the physicians of every civilized country, and there soon developed a wealth of literature upon the subject. Many excellent works were published by French, German and English writers.

The question about which there was perhaps the greatest difference of opinion was whether diphtheria and membranous croup were identical affections, or whether they constituted two distinct morbid processes.

The study of microörganisms in their relation to this disease dates back over a period of many years, more than a half century. In 1868

Oertel, together with Buhl and Hueter, discovered bacteria in the false membrane, the blood and in certain tissues of patients, which he believed sustained a causal relation to the disease. He described these organisms as presenting various forms, such as spherical, rod-like and corkscrew-shaped. They were also demonstrated by von Recklinghausen, Nassiloff, Waldeyer, Klebs, Eberth, Heiberg and others. While these investigators were evidently working along the right lines, and may have seen the specific bacillus, yet they failed to differentiate it from its associates.

The credit of discovering the true bacillus of diphtheria belongs to Klebs, of Zurich. It is generally stated that this discovery was made in 1883, but Lennox Browne makes the following statement in reference thereto: "Professors Hamilton and Sternberg have drawn attention to its discovery by the same observer (Klebs) and to publication of the fact at a congress held at Wiesbaden so far back as the year 1875. The circumstance appears to have attracted but little attention, notwithstanding that on examination of the original reference it is found that Klebs had announced at this date that he had not only detected the bacillus, but that he had also made an effort to cultivate it, and, as far as one can judge, successfully. To Klebs, therefore, the credit of having discovered this organism is undoubtedly due. But since he never definitely announced that he had been able to obtain pure cultures of it, it must be said that he failed in establishing its causal relationship to the disease."

This relationship was later established in 1884 by Loeffler, who succeeded not only in obtaining pure cultures of the bacillus, but also in proving its specific character by communicating diphtheria to guinea-pigs and birds by inoculating them with this organism. Hence, through the combined labor of these two investigators, in discovering and establishing the specificity of this microörganism, it is known by the name of Klebs-Loeffler bacillus. This discovery has had the effect of settling the long and often animated controversy as to whether diphtheria is primarily a constitutional or local affection in favor of the latter, and has placed the study of the disease on a scientific basis.

Working in the immortal Pasteur's laboratory, two of his beloved pupils, Roux and Yersin, in 1889, discovered the devastating toxin produced by the Klebs-Loeffler bacillus.

Within a year von Behring and Kitasato announced diphtheria antitoxin. Ehrlich standardized it in 1897. Theobald Smith a few years later suggested toxin-antitoxin for preventive use, and von Behring applied it in 1912, rivalling his own earlier achievement in producing antitoxin.

In 1913 Schick published his test to visually demonstrate the individual's susceptibility to diphtheria, and, with this as a guide and their extensive opportunities, Park and his co-workers (principally Zingher and Schroder) have been foremost in establishing diphtheria prevention on a rational workable basis, in this country at least.

THE ETIOLOGY OF DIPHTHERIA.

In considering the causation of diphtheria in the light of our present knowledge, it might be thought sufficient to give simply a description of the Klebs-Loeffler bacilli and the associated bacteria, with an explanation of their causative relation to the local and systemic manifestations of the disease. This is the course pursued by many writers of the present day. But while it is impossible to convey a correct knowledge of the etiology of diphtheria without carefully describing its bacteriology, yet for a comprehensive understanding of the subject, it is necessary also to consider the predisposing causes as well as the means by which the disease may be disseminated, and the conditions favorable for its spread.

Not infrequently diphtheria has been communicated by direct contact with detached pieces of exudate or the secretions from the throat and nose of patients. We have known nurses to show symptoms of the disease within forty-eight hours after having had coughed into their faces some of the infectious material from the throats of patients. We have likewise known infection to result from kissing. More than one physician has fallen a victim to diphtheria through his zealous efforts to save the life of a patient by clearing out an obstructed tube after tracheotomy by suction, or by trying to inflate the lungs after the operation by blowing his own breath into them through a tube. Oertel says: "In this way Otto Weber, Seehusen, Valleux, Blache, Cillite fell sacrifices to their professional devotion. Dr. Wiessbauer, of Munich, lost his child, who had a short time previous to its death unfortunately gotten hold of a cannula and put it in its mouth, the cannula having just been removed from a patient sick with diphtheria.

It is well known that diphtheria, like all contagious disease, sometimes occurs sporadically, at other times endemically and then again epidemically. In attempting to explain these circumstances one must take into consideration not alone the *causa causans*, or the specific germ of the malady, but also the *causa efficiens*, or that which determines the occurrence of widespread epidemics. In studying the latter it is necessary to inquire into the sanitary surroundings of each particular locality where the disease prevails, and into all conditions which may influence individual receptivity to the infection, such as climate, domestic environment, age, sex, rainfall, season, etc.

Geographical Distribution, Incidence and Mortality.—No country can be said to be absolutely exempt from diphtheria, although it prevails to a much greater extent in some places than in others. The disease has invaded both hemispheres, and it has occurred in the northern and southern portions of each. Altitude seems to exert but little influence over its spread, as it has been found in both high and low-lying countries. According to statistics of the United States, however, it has caused the greatest proportion of deaths in the Southern Central Appalachian region, the Central Appalachian region and the region of the

Western plains, while the proportions of deaths was least in the South Atlantic coast region and the Gulf coast region.

The disease occurs in the higher degrees of latitude; but of all localities it is most common in the temperate zone and that part of the frigid zone immediately adjacent thereto and least common in the tropics. The records of India show that it is rare in the tropical climate of that country; nor does it thrive anywhere in the tropical parts of Asia. It is also rare in Central and South America.

A great reduction in the incidence and mortality of diphtheria has taken place throughout the civilized world since the introduction of antitoxin treatment. At the same time it is evident that the decline has not been uniform in all countries. In the United States diphtheria death-rates in the years preceding the introduction of antitoxin were considerably higher than those in Great Britain for the corresponding period. A much larger proportional reduction in the diphtheria death-rate seems to have occurred in the United States than in Great Britain in recent years. A comparison of Germany and Great Britain shows a similar relation; the 1924 rates were proportionately much lower in the German than in the British cities, while during the decade 1880-1890 the reverse was true. It is remarkable that three European cities—Southend, England, Toulouse, France, and Geneva, Switzerland—reported not a single death from diphtheria for the year 1924. Another point worth noting is that the Scottish cities Edinburgh, Dundee and Glasgow, which had relatively low rates from typhoid, had relatively high rates from diphtheria. This corresponds to the general prevalence of these two diseases in the United States. From 1910 to 1920 little improvement could be demonstrated in diphtheria mortality in most cities in the United States. In 1910–1914 only 13 cities averaged rates under 10; in 1915–1919 and again in 1920–1924 there were only 18 cities that could be so classed; but in 1924 there were 37 and in 1925 49, with diphtheria-rates practically unknown anywhere before 1910. There can be little doubt that the amazing reduction in recent years is to be attributed in large part to the increasing immunization of school children with toxin-antitoxin mixtures or with anatoxin (toxoid). This conclusion seems warranted, not only by the observations in individual cities like New York, where the method has been extensively employed, but by the rapid decline in diphtheria mortality throughout the general population. In 1923 the diphtheria death-rate in the large cities of the United States was 13.14; in 1924 it was 11.15; in 1926, 9.88. Something may doubtless be credited to the curative side, since the use of antitoxin is probably more widespread and more effective each year; but the fact that since immunization measures began to be applied the diphtheria-rates, previously almost stationary, have suddenly and decisively dropped indicates that the latter is the main factor. If the improvement of the last three years continues diphtheria may well be an almost negligible factor in the mortality returns of 1930.

Season.—Diphtheria is undoubtedly much more prevalent during the cold-weather months than during the summer. The following table shows for the United States the deaths by months from diphtheria in the census year 1900:

Months.	Deaths.	Months.	Deaths.
January	1846	July	827
February	1496	August	898
March	1411	September	1303
April	1156	October	1739
May	1081	November	1912
June	795	December	1904

This table indicates that diphtheria (including croup) is most prevalent in the United States during the nine months, beginning with September and ending with May, and least prevalent during the summer months of June, July and August. The three months showing the greatest number of deaths are November, December and January.

By dividing the year into quarters, representing the four seasons, we find the number of deaths for each season to be as follows: Spring, 3648; summer, 2510; autumn, 4954; winter, 5246. The winter months, and especially the autumn and winter months, show by far the greatest proportion of deaths.

It will be noticed here that the autumn and winter months furnished by far the largest number of cases. This is in accordance with the observation of many writers. Newsholme says: "Diphtheria is most prevalent in autumn and in the early winter months, when the optimum temperature and the optimum degree of humidity of the soil are rapidly disappearing or have departed. It is also most prevalent after the wet weather, occurring in or immediately following exceptionally dry years. Both these conditions tend to raise the ground water and to drive out any pathogenic microörganisms from the soil."

The greater prevalence of diphtheria during the cold-weather months can be rationally explained, we believe, by the well-known observations that the fauces and upper air passages are then much more liable to attacks of catarrhal inflammation, thus affording an increased susceptibility to the disease, and that the sanitary surroundings in schools and dwelling-houses at this time of the year are apt to be at their worst.

Domestic Environment.—Under this head might be included the unsanitary conditions of domestic life, such as result from the crowding together of a large number of people into tenement houses, narrow streets, courts and alleys, where, besides the crowding, the drainage is bad, and the air almost necessarily impregnated with animal emanations and all kinds of foul odors. Surroundings of this nature are sure to prejudice health and exert a definite influence in determining an outbreak of diphtheria and favoring its spread. It is a matter of common observation in all large cities where this disease is endemic that the inhabitants of such localities suffer to the greatest extent. While persons who live under more favorable circumstances are not

spared, yet the transmission of the infection is particularly favored by poverty and uncleanliness.

Not alone do overcrowded conditions of dwelling-houses favor the propagation of diphtheria, but in all congested institutions, especially those for the care of children, in factories, schools, barracks and, in short, wherever there is a large aggregation of persons living under unhygienic environments, there the disease is wont to break out and assume an epidemic form. But, as already stated, more favorable modes of living do not ensure safety against the ravages of the malady. Oertel very truly says: "Robust children who enjoy the best of care and nourishment are seized and carried off by the disease, although the number of such cases does not reach that attained in other classes, in which poverty and uncleanliness favor the spreading of the pestilence." Even the rich and cultivated dwellings, under the most modern sanitary improvements of ventilation, plumbing, drainage and the like, have furnished a fair quota of victims to this fell destroyer of human life. This shows that the specific organism of diphtheria is no respecter of persons; nevertheless, certain environments or conditions of life exert a very potent influence over the spread of the disease.

Dissemination of the Infection.—The infection of diphtheria is commonly communicated through direct exposure to a person suffering from the disease. The dust from a sick-room, contaminated with particles of dried secretions from the throat and nose of a patient, may serve to convey the infection for a short distance through the agency of the atmosphere. The well members of a family in which the disease exists often unwittingly carry the contagium to others. It is frequently disseminated, especially where no attention is given to disinfection, by means of infected articles, such as clothing, bedding, towels, handkerchiefs, carpets, drapery, upholstery, books, toys and the like. It must be admitted that physicians and nurses are sometimes the agencies of transmitting the infection. Even pet animals may play a part in this baneful work.

Doubtless the disease is often spread by exceedingly mild cases—so mild, indeed, that the symptoms are not correctly interpreted. Of course, no restrictions are placed on the movements of persons thus mildly afflicted. Adults continue at their daily vocation, and children go to school as usual. Such cases are constantly met with, especially in large cities where diphtheria is endemic. It is well known that some cases of chronic rhinitis are really of a diphtheritic nature, inasmuch as the Klebs-Loeffler bacilli are sometimes found in this disease. When this condition exists it is frequently not recognized, and, therefore, no restrictions are enforced, nor even any precautionary measures advised. Really, it is a question whether the mild and unrecognized cases of diphtheria are not much more often responsible for the spread of the disease than the severe cases, for the latter are usually surrounded with the proper sanitary measures, such as isolation, disinfection and the like. Yet it should not be overlooked that after recovery from a

well-marked attack patients not infrequently leave their homes and associate with the public before their throats are free from the bacilli. Experience shows that these organisms sometimes remain in the nose and throat in a virulent form for five or six weeks, and at times much longer, after the clinical symptoms have disappeared. Then again, it is not impossible for the disease to be spread by well persons in whose throats the bacilli are present. It has been estimated, by an able observer, that these organisms may be found in the throats of about 2 per cent of all well persons.

Milk has been charged with spreading diphtheria. In order that it should play this role the infection must be introduced through outside contamination. Once introduced, bacilli will find in milk a good culture medium in which to grow and multiply. In the reports of the majority of epidemics which were believed to have been caused by the milk supply, it is stated that either diphtheria prevailed at the dairies or the milk cans were washed with contaminated water. In some instances it is said the cows showed on their teats and udders inflammatory conditions.

In 1922 Graham and Golaz[1] reported that 52 individuals acquired diphtheria in Austin, Texas, from milk sold by a dairy, one of whose employees had a chronic diphtheritic ulcer of the nose. None of these died, because antitoxin was promptly administered in effective doses. It seems to show the importance of the milkman and to indicate that he of all persons on whom the public depends for food should be the cleanest and the healthiest. A simple method of control would be to require him to undergo a physical examination every two or three weeks, or at least as often as once a month. Legislation to this end would be unnecessary if those who supply us with milk realized their responsibility in the matter and adopted this or some such method of eliminating carriers.

Schools are commonly regarded as an important factor in the spread of diphtheria. It is a matter of observation in large cities where the disease is constantly present that the number of cases increases soon after the opening of the schools in autumn, and that the number is smallest during the summer vacation. The rules created and enforced by health authorities, excluding from school all children suffering from sore throats and all those from families in which diphtheria exists, have done much to limit the spread of the disease. But in spite of this wise sanitary measure, it not infrequently happens that children attend school while suffering from mild and unrecognized forms of diphtheria, or, at least, in whose throats virulent bacilli are present. Outbreaks of the disease in certain districts may often be explained in this way.

On the contrary, efforts have been made to show that congregation in schools is not a common cause of epidemics. In support of this

[1] Jour. Am. Med. Assn., 1922, **79**, 1300.

negative view, it has been pointed out that the mortality from diphtheria is by far the greatest among children under five years of age, who have not yet arrived at the school age. It has been stated also that there frequently is a great increase of its prevalence in schools immediately after a holiday recess. The latter statement is undoubtedly true of boarding schools and kindred institutions; but when diphtheria breaks out in such a school it is apt to cause not only a local epidemic, but so great alarm among the pupils as to occasion a stampede, and thus the disease is often widely disseminated. When the infection is introduced into a family it is not surprising that the younger children—those who have not yet attained the school age—should be the principal sufferers. Therefore, the fact that the greatest mortality is found to be among children under five years of age does not invalidate the view that schools operate as an important factor in spreading diphtheria.

Constitutional Predisposition.—The presence of catarrhal affections of the mucous membrane of the nose and throat seems to increase the liability to diphtherial infection. Children who suffer from adenoid growths in the pharynx, with chronic inflammation of the naso-pharyngeal region and from enlargement of the tonsils are regarded as being particularly susceptible to the infection. When these conditions exist together they usually cause what is known as mouth-breathing, by which act the air, instead of being warmed and filtered by passing through the nares, goes direct to the fauces cold and irritating and, perhaps, laden with germs.

Everyone knows that the first evidence of diphtheria is commonly seen on the tonsils. It would, therefore, appear that these glandular organs were the most vulnerable part of the body for attack by the Klebs-Loeffler bacilli. The peculiar anatomical structure of the tonsils, having on their exposed surface deep crypts or lacunæ into which the organisms may lodge and multiply, affords a very probable explanation why they are so often the seat of the disease process. When these glands are inflamed and swollen the lacunæ become deeper and the mucous covering so delicate that they have been not inaptly compared by Virchow to open wounds. Hence, it is easy to see how this condition may increase susceptibility to diphtheria.

Certain other diseases with anginose manifestations also furnish a marked predisposition to diphtheria. Of these we would mention particularly *scarlet fever* and *measles*. The frequency with which the Klebs-Loeffler bacilli are found in the throats of scarlet-fever patients is really astonishing; according to our experience at the Philadelphia Hospital for Contagious Diseases, they are present in 10 to 33 per cent of all cases. Indeed, they are often found when the clinical conditions would not suggest the existence of diphtheria. These two diseases, however, not infrequently coexist, the symptoms peculiar to each appearing at the same time. But symptoms of diphtheria may develop during the course of scarlet fever or during convalescence.

It is also possible for diphtheria and Vincent's angina to occur coincidently, although great care is required in making a diagnosis of this kind, since diphtheroid bacilli may be found in the exudate of Vincent's angina without signifying the presence of diphtheria and conversely, a few spirochetes and fusiform-like bacilli may be found in diphtheritic exudates without signifying the coexistence of Vincent's angina.

As might be expected from what has already been said, the catarrhal affection of the fauces and upper air passage incident to measles renders the individual very responsive to the action of the diphtheria bacillus. Membranous croup associated with measles is by no means an infrequent occurrence, and, moreover, is exceedingly fatal. When measles prevails in Philadelphia we have numerous applications for the admission to the Philadelphia Hospital for Contagious Diseases of cases complicated with membranous laryngitis. Many of them belong to the true type of diphtheria, but others, it must be admitted, are probably caused by other bacteria, as the diphtheria organism is not always found.

Recurrent Attacks.—In most infectious diseases one attack usually confers immunity against subsequent attacks. This is particularly true of measles, scarlet fever and smallpox. But with regard to diphtheria this announcement cannot be made with equal stress, as *recurrent attacks* are by no means rare. We have frequently seen patients suffer from a second attack before leaving the hospital. Also children have been admitted to the hospital a second time, and, in two or three instances, a third time, suffering from diphtheria, after intervals of a few weeks to three or four years.

Age.—The diphtherial infection finds in children the most favorable soil for its reception and propagation. The disease is exceedingly common among children up to the age of ten years, but those from one to five years are most susceptible. Some writers state that diphtheria attacks but seldom infants under one year of age, and that in the first half year of life there is complete immunity to the disease. It has fallen to our lot to see a large number of infants suffer and perish from this scourge, and many of them were under the age of six months. We believe, however, the infection is not so readily received at this early age. Adults not infrequently acquire the disease; but their chance of escaping it or of recovering when attacked is much greater than is the case with children.

It is recognized fact that in all epidemics of diphtheria as well as in endemics children are the first to suffer from the disease. They also furnish the principal part of the mortality. This will be considered more fully under the head of prognosis. It is worthy of notice that the laryngeal form of diphtheria is limited almost entirely to children.

The following table shows the diphtheria patients admitted to the Philadelphia Hospital for Contagious Diseases during 1893–1902, classified into age groups:

Year.	Under 1 year.	1 to 5 years.	5 to 10 years.	10 to 15 years.	15 to 25 years.	25 years and upward.	Total.
1893	3	82	53	18	36	25	217
1894	16	218	120	31	52	28	465
1895	25	327	187	46	56	65	706
1896	33	404	276	71	49	36	869
1897	34	560	437	126	89	49	1295
1898	42	552	447	93	47	48	1229
1899	38	659	462	102	62	50	1373
1900	40	595	473	117	90	52	1367
1901	30	374	287	106	56	36	889
1902	38	305	159	40	33	26	601
Total	299	4076	2901	750	570	418	9011

This table bears out the statement that children from one to five years of age are most susceptible to diphtheria, and also shows that the susceptibility diminishes very considerably after the age of ten years. We would direct attention to the table as showing the large number of infants that have come under our care. As parents are naturally loath to send children of this tender age to a hospital it is not improbable that the table shows a smaller proportion of patients under the age of one year than if the entire number in the city were considered.

Sex.—It scarcely seems probable that sex should exert any influence over susceptibility to diphtheria. It has been stated, however, by some observers that up to the age of four years there is no difference in susceptibility, but subsequent to this age males suffer more frequently than females.

The 1900 census report of the United States shows that for the census year the deaths were quite equally distributed between the two sexes -14,878 were males and 14,081 were females. This very extensive statistical evidence warrants the conclusion that predisposition to the disease is not influenced by sex, and that where any disparity is found it is accidental rather than otherwise.

THE BACTERIOLOGY OF DIPHTHERIA.

Fortunately the morphological characteristics of diphtheria bacilli are so pronounced that with little experience they are readily recognized in stained smears of cultures; in smears of exudate their recognition is more difficult. But it is important for physicians not in ready access to laboratories to have a good working knowledge of the bacteriology of diphtheria because of the great aid afforded in the *prompt* diagnosis of the disease. An expensive equipment is not necessary—a microscope with an oil-immersion lens, Loeffler's blood-serum medium and a few stains are the essentials; for an incubator the vest pocket or any warm place will suffice since the bacillus grows well at 32° to 35° C.

Morphology.—The diphtheria bacillus is a straight or slightly curved, rod-shaped organism with rounded ends; the diameter is ordinarily from 0.5 to 0.8 microns and the length from 2 to 3 or more microns.

FIG. 125.—B. diphtheria agar culture. Bacilli small and uniform in shape. × 1000 diameters. (Park.)

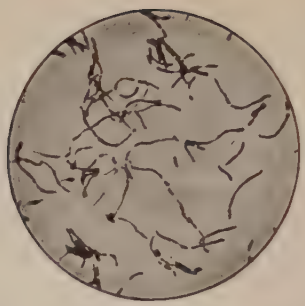


FIG. 126.—Extremely long form of diphtheria bacillus. This culture has grown on artificial media for thirty years and produces great amounts of toxin. × 1100 diameters. (Park.)

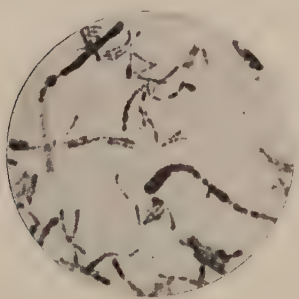


FIG. 127.—B. diphtheriæ. Forty-eight hours' agar culture. Many segments; long, Indian-clubbed ends. One year on artificial media. × 1410 diameters. (Park.)

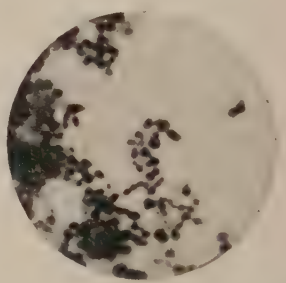


FIG. 128.—B. diphtheriæ. Twenty-four hours' agar culture. Coccus forms. Segmented granular forms on Löffler's serum. Only variety found; in cases of diphtheria at Children's Home. × 1410 diameters. (Park.)

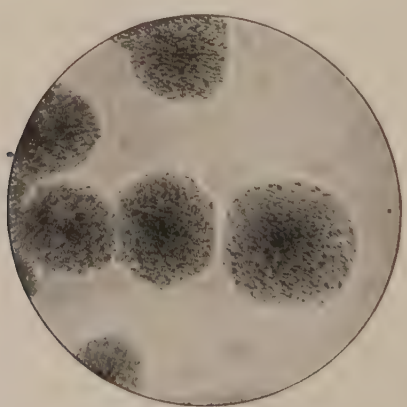


FIG. 129.—Colonies of diphtheria bacilli. × 200 diameters. (Park.)

It is subject to the greatest variation of form; this is true to such an extent that polymorphism is an important characteristic.

In 1900 Wesbrook read before the Association of American Physicians a carefully prepared article on the various morphological types of diphtheria bacilli. He divided them into three groups—the granular (those with deeply staining granules), the barred (those with transverse bands) and the solid or evenly staining forms. Further subdivisions of these groups were discussed.

The granular type of bacillus is the one most commonly seen in the beginning of the disease; later these give way wholly or in part to the barred or solid forms; solid types may sometimes be replaced by the granular when convalescence is established and just before the throat begins to clear.

The relation of the solid forms to true diphtheria bacilli is still unsettled. They are said to be sometimes encountered as variants in pure cultures of diphtheria organisms. Certain of the solid forms have characteristics which seem to distinguish them from the diphtheria bacillus and to class them with the pseudo-diphtheria organisms. For instance, some of the solid forms fail to produce acid in dextrose bouillon, a property which is possessed by the true diphtheria bacilli.

By means of the complement-fixation test Kolmer[1] found that the Hofmann bacillus was probably related to the true diphtheria bacillus but a "mutant" capable of transmitting its qualities from generation to generation. Smith[2] and Bailey[3] have likewise failed to group diphtheria bacilli by the agglutination test, but Hammerschmidt[4] states that he has been able to classify them into five groups, and Rosenow and Bailey[5] state that there is a wide immunological gap separating virulent and non-virulent strains.

Fortunately the toxin of different virulent bacilli appears to be identical for all, so that the antitoxin produced by the immunization of horses with a single toxin is capable of neutralizing all diphtheria toxins.

Staining Properties.—The diphtheria bacillus stains well with the ordinary aniline dyes and with the Gram stain. The best results are are, however, obtained with Loeffler's alkaline solution of methylene blue, which brings out the granules well. This solution is made up of:

Concentrated alcoholic solution of methylene blue	30 cc.
Caustic potash in 1 to 10,000 solution	100 "

The stain suggested by Neisser in 1897 aids one to overcome in a very large part the difficulty occasionally experienced in differentiating the diphtheria bacillus from other throat organisms which may simulate it. The method is as follows: The culture to be tested should be grown upon Loeffler's blood-serum medium, it should

[1] Jour. Infect. Dis., 1912, **11**, 44.
[2] Jour. Hyg., 1923, **22**, 1.
[3] Jour. Immunol., 1925, **10**, 791.
[4] Deutsch. med. Wchnschr., 1924, **50**, 1831.
[5] Jour. Infect. Dis., 1925, **37**, 97.

develop at a temperature not lower than 34° C. and not higher than 36° C., and it should be not younger than nine and not older than twenty-four hours. A cover-glass preparation made from such culture is stained for from one to three seconds in the following solution:

Methylene blue (Grübler's)	1 gm.
Alcohol (96 per cent)	20 cc.

When dissolved, mix with:

Acetic acid	50 cc.
Distilled water	950 cc.

After thoroughly rinsing in water the preparation is then stained for from three to five seconds in vesuvin (Bismarck brown), 2 gm. dissolved in a liter of boiling distilled water, filtered and allowed to cool. It is again rinsed in water and examined as a water-mount or dried and mounted in balsam.

When so treated the bacilli appear as faintly stained brown rods in which from one to three brown granules are always to be observed. The dark granules are at one or both poles of the cell, are more or less oval, and usually seem to bulge a little beyond the contour of the bacillus in which they are located.

Biological Characters.—The diphtheria bacillus is aërobic, non-motile and liquefying, and does not form spores. It grows freely in the presence of oxygen, but is also a facultative anaërobic (Sternberg).

The diphtheria bacillus is destroyed by exposure to a temperature of 58° C. (136° F.) for ten minutes. In the dried state it may maintain its vitality for a long period. Park found active bacilli on dried membrane after seventeen weeks, and Roux and Yersin living but non-virulent bacilli after five months. Bacilli were found by Abel to persist for five months on children's toys kept in the dark. When the organisms are preserved in sealed tubes and protected from light and heat they may remain virulent for years.

Loeffler's serum medium is the best for the growth of the diphtheria organism and the one which is ordinarily employed for the culture test. It is a mixture of 3 parts of blood serum with 1 part of bouillon, containing 1 per cent of peptone, 1 per cent of grape-sugar and 0.5 per cent of sodium chloride.

The diphtheria organism grows so much more promptly upon this mixture than other mouth and throat bacteria that at the end of twenty-four hours the diphtheria colonies may be readily recognized while the other colonies are still inconspicuous.

Typical diphtheria bacilli are capable of fermenting many sugars and especially dextrose and dextrin; as stated by Kolmer and Moshage,[1] they are especially likely to be toxin producers. On the other hand, cultures totally unable to ferment sugars are usually non-virulent and likely to be Bacillus hofmanni.

Pathogenesis.—According to Park the diphtheria bacillus is pathogenic for guinea-pigs, rabbits, chickens, pigeons, small birds and cats;

[1] Jour. Infect. Dis., 1916, **19**, 19, 28.

to a less extent it is pathogenic for horses, cattle, dogs and goats, but not for rats and mice. The rat and the mouse exhibit a remarkable insusceptibility; a dose of 2 cc. of a bouillon culture will kill a rabbit, but not a mouse.

The inoculation of such animals as cats and rabbits by rubbing a pure culture of the diphtheria bacillus upon the mucous surface of the opened trachea produces a disease which is essentially the same as that seen in man. The animal usually dies in from two to four days, not from a general invasion by the diphtheria organism, but as a result of the absorption of the soluble toxins formed at the seat of infection.

In animals that did not die too quickly Rous and Yersin have noted the development of paralysis of the posterior extremities.

It is a well-established fact that the diphtheria bacillus under ordinary circumstances remains in the vicinity of the site of inoculation. When it is found in the blood or visceral organs its presence is probably accidental. The widespread changes in important organs in diphtheria must, therefore, be ascribed to a diffusible circulating poison produced by the diphtheria organism in its original nidus. That such is the case was proved by Roux and Yersin in 1888, when they demonstrated the presence of a poison in diphtheria cultures which were filtered through porous porcelain. It was found that old cultures and particularly those of alkaline reaction, had a much greater toxic potency than recent cultures of acid reaction. Injection of filtered cultures into susceptible animals produced local edema, congestion and hemorrhage of the internal organs, effusion into the pleural cavity, etc. It is thus seen that practically all of the symptoms produced by the injection of pure cultures of bacilli may be obtained by injection of the filtered cultures save the production of a false membrane.

Virulence and Avirulence of Diphtheria Bacilli.—When virulent bacilli are grown in bouillon, soluble toxins are developed which produce certain noxious effects upon guinea-pigs. Even where the bacilli are removed by filtration the injection produces death of the animal. Practically all bacilli derived from clinical cases of diphtheria produce toxins with these properties. Conversely, it would seem that bacilli that produce no toxins in bouillon will not produce them in the human subject.

Formerly the non-virulent bacilli were classed by some writers in a group apart from the genuine diphtheria organism. It is now pretty generally recognized that true diphtheria bacilli may possess varying grades of virulence. Those occurring in the throats of convalescent patients and those found in the throats of healthy persons have frequently a very low grade of virulence. The less virulent forms commonly increase in numbers as progress toward the recovery of diphtheria advances.

Technique and Practical Value of Guinea-pig Virulence Tests.—Young guinea-pigs weighing from 250 to 300 gm. are quite susceptible to diphtheria toxin, and are used in determining the strength of a toxin

and in standardizing antitoxin. The test may be of great value in the management of convalescent and "carrier" cases of diphtheria, harboring bacilli in the upper air passages, in determining whether the microörganisms are dangerous or merely harmless non-pathogenic saprophytes. It is practically impossible, from the morphology of the organism alone, to decide whether or not a given culture is dangerous, and prolonged quarantine may not only be irksome and inconvenient, but if the organisms are proved to be harmless it is unnecessary as well.

To be reliable, however, such a test must be carried out very carefully. In the case of a highly virulent culture the mere introduction of a few organisms beneath the skin will suffice to demonstrate their dangerous character, but with cultures only slightly virulent more care is necessary, for although the patient may show no ill-effects as a result of the presence of the bacilli, in the throat of another and less immune individual they may be highly dangerous.

The following method has been used by one of the authors in many hundreds of such tests, and has proved of distinct value:

1. Make a culture of the part harboring the bacilli on a tube of Loeffler serum medium. Incubate at 35° C. for from eighteen to twenty-four hours; prepare a smear and stain with Loeffler's methylene blue. If diphtheria bacilli are present they must be isolated in pure culture. *Never attempt a guinea-pig test with an impure culture.*

2. Isolate by the "streak" method on plates of blood serum.

3. Inoculate a tube of 1 per cent glucose bouillon, which is neutral or slightly alkaline, with *several different colonies.*

4. Incubate at 35° C. for three days, keeping the tube in a slanted position in order to give the culture as much oxygen as possible. If a good growth does not appear in twenty-four hours transplant to another tube of bouillon until the bacilli have been "educated" to grow on the medium.

5. Examine for purity. Select a 250- to 300-gm. guinea-pig and inject 2 cc. of the unfiltered culture in the median abdominal line. Animals over the weight specified are more resistant and less reliable for the test. The unfiltered culture is used, since toxin is but one element of the disease-producing power of diphtheria bacilli, and toxin production in bouillon may not be a true index of the toxin production in mucous membranes.

6. Carefully observe the animal for at least four days. Even slight toxemia, especially if accompanied by edema at the site of injection, should be regarded as a positive result.

7. After death perform a careful autopsy. Make cultures of the edematous area, peritoneum and heart blood. Diphtheria bacilli may be found in the edematous fluid, but will rarely be found in the peritoneum or in the blood. Observe whether acute hyperemia of the suprarenal glands is present.

8. Not infrequently animals showing mild or even an absence of the symptoms of toxemia develop paralysis of the hindquarters two or

three weeks later. According to Ehrlich, this paralysis is due to the action of "toxon," a toxic substance secreted by the bacillus or, as believed by others, a modified form of toxin.

9. To prove that diphtheria was the cause of the toxemia or death mix 2 cc. of the culture in a test-tube with 1 cc. of diphtheria antitoxin (800 units). After standing aside for an hour at room temperature inject the mixture subcutaneously in the median abdominal line of a 250- to 300-gm. guinea-pig. Symptoms of toxemia do not develop.

In a comparative study of the above and other methods, Kolmer and Moshage[1] found that washing off a pure culture from a slant of Loeffler's blood serum media with 10 cc. of sterile salt solution, emulsifying and injecting 4 cc. subcutaneously in the median abdominal line of a 250- to 300-gm. guinea-pig yielded equally delicate results. The intracutaneous method of Neisser, which has also been advocated by Zingher and Soletsky,[2] while being more economical, in that 2 pigs suffice for 4 or even 6 tests, was found to yield somewhat indefinite reactions with bacilli of low virulence.

Kolmer, Woody and Moshage[3] have found the guinea-pig inoculation test a valuable practical procedure and state that "for the proper management of diphtheria according to bacteriological examinations, an effort must be made to differentiate between the harmful and harmless bacilli. For instance, a 'carrier' may be quarantined forever if guided by the fact that the presence of a diphtheria-like bacillus means diphtheria. The medical attendant must be convinced of the value of bacteriological examination and of the earnest efforts of the bacteriologist to work with him both in the interests of his patient and for the public welfare. The practitioner must be taught not to be afraid to report all of his cases and to culture faithfully. If, however, bacteriological examinations serve to give unnecessary embarrassment to the practitioner by quarantining 'carrier' cases, or by maintaining a quarantine unnecessarily long after convalescence as a result of conscientious efforts on the part of the latter to do his duty in taking cultures, he is not likely to give his best coöperation, and without this no real good is possible."

In the Philadelphia Hospital for Contagious Diseases in all instances in which the virulence test is negative the patient is considered noninfectious and fit for release from quarantine, regardless of what the cultures may show. These cases have been followed closely and the number of "return" cases has become practically negligible. On the other hand, we have on several occasions observed that convalescent children harboring virulent bacilli as determined by animal inoculation test, but subsequently released from quarantine on the basis of two or three negative cultures, have been responsible for the infection of others.

The results have shown quite definitely that the virulence test is the safest and nearest perfect method that has been devised, and

[1] Jour. Infect. Dis., 1916, **19**, 1.
[2] Ibid., 1915, **17**, 454.
[3] Am. Jour. Dis. Child., 1926, **11**, 257.

regardless of all things else, in the face of negative guinea-pig test, the patient is discharged; in the face of a positive test he is detained.

If the physician will take cultures carefully, conscientiously and freely, especially several cultures, before excluding the diagnosis of diphtheria in a given case, and if three consecutive negative cultures are required instead of two before quarantine is lifted, combined with the efforts of the bacteriologist to differentiate between virulent and non-virulent bacilli, with the judicious use of the animal inoculation test in suitable cases, we believe that the bacteriological diagnosis and management of diphtheria will be efficient and satisfactory to all. Kelly and Potter[1] have also found the test of value in administrative work in diphtheria.

The Distribution of Diphtheria Bacilli in the Body.—General infection with the diphtheria bacillus has been reported by a considerable number of writers.

Frosch[2] was the first to note the presence of diphtheria bacilli in the internal organs of patients dead of diphtheria; he found them in the heart's blood, liver, spleen, kidney and lymph nodes in 10 out of 15 cases examined.

Kutscher found the bacilli in 8 out of 9 cases in the lung. Kanthack and Stevens found them in the spleen in 10 out of 21 cases, in the kidney in 2 out of 3 cases and in the lungs in each of 26 cases.

Wright and Stokes, in a report of 31 cases, found the diphtheria organism 30 times in the lungs, 9 times in the liver, 7 times in the mesenteric lymph nodes, 5 times each in the spleen and heart's blood, 4 times in the cervical lymph nodes and twice each in the brain and bronchial glands.

Genersisch examined 25 cases of septic diphtheria, in some of which he failed to find the streptococcus in the blood or internal organs; he concluded that the diphtheria bacillus was capable alone of producing septic symptoms. Stephens and Parfitt have reported a case of general infection with the diphtheria bacillus in which these organisms were recovered from the blood during life. In a child with an unusually high and unexplained temperature, suffering from diphtheria at the Philadelphia Hospital for Contagious Diseases, we recovered the diphtheria bacillus in pure culture from the blood a day before death.

Councilman, Mallory, and Pearce have extensively cultured the various organs in 161 diphtheria autopsies. They found bacilli in the heart's blood in pure culture 7 times and 4 other times in association with other organisms. Diphtheria bacilli were found in the liver 30 times, in the spleen 19 times and in the kidney 27 times. These investigators remark, *apropos* of these findings: "Whether the diphtheria bacillus does or does not continue to produce the toxic products wherever it may be in the blood or internal organs it is impossible to say, but from the number of fatal cases with such an infection, it

[1] Jour. Am. Med. Assn., 1923, **81**, 734.
[2] Ztschr. f. Hyg. u. Infect., 1893, **13**, 49.

would seem very probable that it does." Kanthack and Stephens, and Genersisch also, incline to this opinion.

Diphtheria bacilli have been thrice found upon the vegetations of an acute ulcerative endocarditis. These have been reported by Howard, Wright and Councilman, Mallory, and Pearce. The antrum and accessory nasal sinuses may harbor diphtheria bacilli for a long time. Wolff, in autopsies on 15 severe cases of diphtheria, found diphtheria bacilli in the antra in 12. Councilman, Mallory, and Pearce examined the antra in 52 cases; in 16 of these diphtheria bacilli were recovered from both sides. They suggest that infection of the antra may explain the persistence of the bacilli in the nasal discharge for protracted periods.

The middle ears were examined in 144 cases. In 86 they were found diseased and in 37 diphtheria bacilli were recovered from one or both ears. They were usually found in association with other bacteria.

Persistence of Diphtheria Bacilli in the Throat.—Virulent bacilli may persist for varying periods in the throats of persons who have recovered from diphtheria. In the vast majority of cases they disappear in from one to two weeks after the disappearance of the membranous exudate. Park and Beebe, in a study of 605 consecutive cases, found the bacilli absent within three days after the disappearance of the membrane in 304; in 176 cases they persisted for seven days; in 12 for three weeks; in 4 for four weeks; in 2 for nine weeks. Later Park saw a case in which the bacilli were found for six months. Le Gendre and Pochon described, in 1895, a case in which the bacilli persisted in the nose for fifteen months after an attack of nasal diphtheria.

Diphtheria Bacilli in the Throats of Healthy Persons.—There are two factors necessary for the production of diphtheria—the presence of the specific bacillus and the existence in the host of susceptibility to the disease. Many persons appear to be able to harbor virulent diphtheria bacilli in their throats without contracting the disease because of the presence of natural antitoxin in the blood. In 1894 Park and Beebe examined the throats of 330 healthy persons who had not, as far as was known, come in contact with persons suffering from diphtheria. Of this number, virulent bacilli were found in 8, 2 of whom later developed the disease. In 24 of the 330 healthy throats nonvirulent or attenuated forms of the diphtheria organisms were found.

There are two classes of persons carrying diphtheria bacilli in their throats—those exposed to the disease and those in whom no exposure is known. Among the general unexposed public about 3 per cent of the people have typical diphtheria bacilli in their throats. In the eastern part of the United States it is 1.39 per cent.

In considering the virulence of the bacilli found in healthy throats it is shown that only about 17 per cent of the 1 to 2 per cent of persons harboring diphtheria bacilli have virulent bacilli which are dangerous to the public health.

Pseudo-diphtheria Bacilli.—Considerable diversity of opinion still exists among bacteriologists at the present time as to the proper classification of certain bacilli which are morphologically and tinctorially identical with the diphtheria organism, but which differ from it in other respects.

Most writers agree that the non-virulent and non-toxic Loeffler bacilli are to be regarded as true diphtheria organisms which have merely suffered attenuation.

There are, however, orther organisms which resemble the diphtheria bacillus very closely, but differ therefrom not only in the absence of toxin production, but also in certain other particulars. Among these may be included the Bacillus hofmanni and the so-called xerosis bacillus, which is commonly found in the eyes in the condition known as xerosis conjunctivæ.

A diphtheria-like bacillus which produces no acid in dextrose and dextrin bouillon cultures, which does not show typical polar granules when stained by the Neisser method, and which will not kill guinea-pigs, may be set down as a pseudo-diphtheria organism. Such a bacillus will not produce diphtheria in the human subject, and its presence in healthy throats and noses need not give concern.

INCUBATION PERIOD.

The period of incubation is the interval between the moment of receiving the infection and the beginning of symptoms. It is believed that this period may vary somewhat according to the activity or virulence of the infecting organism and the receptivity of the individual. When the organisms lodge upon a mucous membrane which is readily penetrated the diphtherial process is apt to appear sooner than where this membrane has greater resistance.

Where the conditions are favorable the bacilli doubtless begin their work as soon as they have effected a lodgment, but changes at the seat of disease are not recognized until the process is sufficiently far advanced to show the characteristic exudate. The constitutional disturbances, such as fever and other subjective symptoms, usually do not appear until the local manifestations have reached a certain degree of intensity. It is quite possible, therefore, that mild cases may not be recognized as early as severe ones, and thus the period of incubation among the former may sometimes appear to be longer.

Some observers believe that this period is shorter during the epidemic prevalence of diphtheria, especially when of a malignant type, than when the disease occurs sporadically. In most cases it is difficult to determine the exact moment of infection. This can only be known when there has been but a single exposure. It would seem that there should be no difficulty in determining the period of incubation from observations in a large hospital, and yet we find that nurses and other attendants who take diphtheria fall ill at variable periods after com-

mencing work. In the vast majority of instances, however, the symptoms of the disease appear during the first week of service. Occasionally a nurse will work for three or four weeks before manifesting any evidence of infection. One of our nurses performed her duties for one year before she fell ill with diphtheria. It is evident, therefore, that the infecting organisms may find in an individual a more favorable soil at one time than at another, and this variation of susceptibility adds to the difficulty of establishing the period of incubation.

There is no doubt, however, that in comparison with most other infectious diseases the period of incubation of diphtheria is relatively short. Most observers fix the period from two to three days; some believe that it may vary from one to eight days, and others allow that in exceptional cases it is as long as twelve to fourteen days. We believe that in the vast majority of instances it is from two to five days.

THE SYMPTOMATOLOGY OF DIPHTHERIA.

Not infrequently the characteristic symptoms of diphtheria are preceded by slight indisposition, such as lassitude, loss of appetite, headache, nausea and sometimes vomiting and general malaise. These prodromes, however, are not distinctly different from what may be seen in many other affections. There may be slight stiffness of the neck, with hypersensitive lymph glands near the angle of the jaw, and a little inconvenience experienced in deglutition. On inspection, the fauces may be found hyperemic. There may be mild chilly sensations, and in children convulsions sometimes occur. The temperature is apt to be only slightly elevated. These mild symptoms rarely continue longer than a few hours before the true nature of the disease is revealed.

Vomiting is by no means so constant a precursory symptom of diphtheria as of scarlet fever. The pain in the fauces and at the angle of the jaw is but slight as compared with that experienced in ordinary tonsillitis. Indeed, the comparative absence from pain at this stage of the disease is of considerable significance in the matter of diagnosis. There may be diarrhea or constipation; one is just as liable to be met with as the other. The fauces often feel dry, and there is a disposition to hawk and clear the throat.

When the disease is going to assume the laryngeal form the voice often at an early stage becomes husky, even before any membrane has appeared. Along with this symptom there is very commonly a shrill, brassy cough, and sometimes slight dyspnea, resulting from a mild spasmodic affection of the larynx.

Throat.—The first positive evidence of diphtheria is usually seen in the throat. As stated under the head of etiology, the tonsils seem to favor the lodgment and propagation of the specific bacilli; for in the vast majority of cases it is on these glands that the disease process

begins. The fauces are commonly red and inflamed, and the tonsils may or may not be swollen, although in most cases the swelling is marked. Small spots of exudate now appear on their surface or in their crypts - the latter being a common seat of this process. In mild cases this condition does not increase. It is then difficult to distinguish between diphtheria and tonsillitis without the aid of bacteriological examination. Patients with the latter affection are often sent to the hospital on a mistaken diagnosis.

In the better-marked form of the disease the small patches of exudate rapidly spread, covering not infrequently the entire tonsillar surface in less than twenty-four hours. This local manifestation may be confined to one tonsil, but more often involves both. When the exudate is limited to the tonsils the liability to secondary systemic infection is not very great.

In the severe forms of diphtheria the exudate spreads beyond the region of the tonsils, or it may appear simultaneously on various parts of the fauces. One of its peculiarities is that it often shows itself as small, thick patches on prominent points, such as the end of the uvula, the edge of the epiglottis, the cartilage of Wrisberg and the like. It very frequently covers completely not only the tonsils, but the anterior and posterior pillars, the pharyngeal wall, the uvula and the entire soft palate. In severe cases it is not uncommon to see the exudate on the vault of the mouth piled up so high as to form a thick, spongy mass, seriously interfering with deglutition. Cases have come under our observation in which not only the entire fauces, including the soft palate, were covered, but even the hard palate and the greater part of the buccal cavity also. Sometimes it appears on the gums, but more often invades the edges of the tongue. It is frequently seen in the pharyngeal vault, and may extend into the Eustachian tubes. The nares and the larynx are so often involved that the behavior of the disease in these cavities will subsequently receive special notice.

The exudate is usually of a yellowish-white or cream color, but it may present a dark-gray appearance. Its color is liable to be changed by the ingestion of certain drugs, or by remedial agents employed locally. It sometimes is rendered darker by having coagulated blood incorporated with it. But in perfectly typical cases it does not look unlike moist chamois skin. Indeed, when large fragments or casts are exfoliated and floated in water they have a strong resemblance to this material.

The exudate may be thick, or thin and filmy. When very thick it may be seen, even at quite an early state, lying rather loosely on the mucous membrane, or partly detached at its margin, especially when located on the soft palate. If forcibly removed it is liable to be reproduced in the course of a few hours, although in many cases it exfoliates quickly and does not reform. Instead of presenting the appearance of a distinct membrane lying upon the mucous surface, the exudate sometimes forms into and becomes a part of the mucous membrane itself.

In this case there is a grayish discoloration which disappears slowly, and often by the process of necrosis, rather than by exfoliation of the membrane. Of course, this process is followed by an ulcerating surface which heals by granulation.

The involved parts of the fauces, especially the uvula, become edematous and swell considerably. After the exudate has disappeared from the uvula the latter is apt to present an ulcerated appearance, and through loss of tissue is not infrequently left smaller than normal. In all severe cases in which there is edema and swelling of the fauces there is not only difficult and painful deglutition, but the respiration and articulation are also affected.

In the act of swallowing it is not uncommon to see milk regurgitated through the nares. As the case progresses the voice becomes distinctly nasal, and is apt to continue so for some weeks.

At first the exudate is free from odor; but when the disease is severe a distinct odor is noticed in the course of two or three days. Indeed, the breath of the patient is often so peculiarly offensive that an experienced clinician might be led to suspect the nature of the affection before an examination of the throat has been made. In septic cases, when decomposition of the secretions and the exudate goes on rapidly, the odor is in the highest degree offensive, and is well calculated to excite suspicion that extensive necrotic changes of the tissues may be taking place. The tissue change, however, is not always as great as the odor would indicate. A copious mass of exudate is often thrown off very quickly by the process of exfoliation, leaving the parts only slightly ulcerated. In such cases the odor will promptly disappear, especially with the use of cleansing or antiseptic lotions. With this apparent improvement one should not be too hasty in pronouncing the patient out of danger, for the probabilities are that the most critical period of the disease is yet to be encountered. Where the mucous lining of the fauces is at all destroyed, leaving the absorbents exposed, the toxin of the specific microörganisms is permitted to enter the circulation, and the subsequent danger from toxemia is far greater than the primary local disease.

While there is usually some swelling and tenderness of the cervical and submaxillary glands at an earlier stage of the diphtherial process, coincidently with intense involvement of the fauces, these glands, together with the surrounding areolar tissue, become indurated and infiltrated, giving rise often to extensive tumefaction. The face, besides being pale and sallow, presents also a swollen and glossy appearance. As the exudate and septic secretions disappear from the throat, the tumefaction of the neck subsides. Occasionally, however, the cervical glands take on suppurative action, but not so frequently as in scarlet fever.

Esophagus.—One peculiarity of the diphtheria bacillus is the rarity with which it infects the esophagus even in severe faucial infections.

But esophageal diphtheria is not unknown. Gonin,[1] for example, has reported a case in which the exudate was found at necropsy even in a part of the stomach, and Stupka is quoted as compiling 9 cases from the literature showing cicatricial stenosis of the esophagus following diphtheria.

Nose.—Next to the fauces the nose is the most common site of the diphtheritic process. The disease not infrequently attacks the nares primarily, but most often the exudate extends from the throat to the nasal cavities by way of the posterior aspect of the uvula. When this occurs the posterior wall of the pharynx is also liable to be involved through contiguity of structure. At first there is but little discharge from the nares, as in the beginning of an acute catarrh, but it soon increases and becomes flocculent. When the disease has fully developed the discharge is often profuse and sometimes fetid.

Before the diphtherial process has continued very long evidence of copious exudation may be seen by inspecting the nares. In many cases the membrane is very thick and dense, and occludes the nasal cavities completely. There is then but little discharge from the external orifices; but the voice becomes distinctly nasal, and the patient is obliged to breathe through the mouth.

When the fauces are at the same time severely involved, the respiration becomes considerably hampered, and there is also difficult deglutition, with marked restlessness and insomnia.

The amount of exudate that is sometimes expelled from the nares is enormous. The membrane is often thrown off in perfect casts, and on inspecting these one is apt to feel surprised that so much material could have been contained within the nasal cavities. When the exudate begins to separate, or has been either partly or wholly cast off, the discharge usually returns, and is often sanguino-purulent in character. There is no form of diphtheria more dangerous than that of the nares. The injury sustained by the capillary bloodvessels prepares the way for rapid absorption of the toxins, the effects of which are apt to become painfully visible in a short time. Not only is systemic poisoning seen, but the more common sequelæ of diphtheria most often follow the nasal form of the disease.

Epistaxis is of frequent occurrence even in mild cases; but when the diphtheritic involvement is intense the hemorrhage from the nose is liable to occur repeatedly, as the disease progresses, and may prove to be a very troublesome symptom. In some cases there is a constant oozing of blood, while in others the hemorrhage is sometimes so free as to be the immediate cause of death.

In the severest form of nasal diphtheria the nose is slightly reddened externally, and moderately swollen or edematous. The face also is edematous, remarkably pale and has a peculiar glistening appearance. The pulse is usually feeble, the circulation bad, vomiting often occurs

[1] Schweiz. med. Wchnschr., 1923, **53**, 625.

and not infrequently there is marked drowsiness. Indeed, the symptoms, taken together, are such as would indicate profound systemic poisoning. Many patients in this condition die at a comparatively early stage of the disease.

In the more favorable cases the exudate is thrown off *en masse* in the form of casts, and the constitutional symptoms do not become so pronounced. But one should not feel too sanguine of recovery in any case, for danger of the development of toxemia is never absent. Even when this serious condition does not arise, and the general symptoms seem most favorable, still there is a strong liability that the affection may be followed by paralysis, either partial or general. Postdiphtheritic paralysis is more common after the nasal form of the disease than after any other variety.

Nasal diphtheria sometimes assumes the form of chronic rhinitis. In such cases there is usually a discharge from the nares and often excoriation of the skin about the nose. But the affection may persist for months, with little or no nasal discharge. Persons thus afflicted often unwittingly spread diphtheria. It is important that such cases should be recognized and treated, and even isolation should be advised until a cure is effected and the specific organisms have disappeared. It is only by the aid of bacteriology that this form of diphtheria can be definitely determined.

Middle Ear.—From the pharyngeal vault the exudate sometimes spreads by way of the Eustachian tube to the middle ear, causing an acute median otitis. This is often unattended by pain, hence, the condition may not be recognized until suppuration takes place and the tympanum has ruptured. The purulent discharge which flows from the meatus will show the presence of the bacilli of diphtheria associated with certain other organisms, such as streptococci and staphylococci. There is usually some rise of temperature, often assuming a septic character.

The otorrhea frequently persists a long time, but is seldom followed by permanent deafness. Temporary deafness, however, may be seen as the result of a paretic condition of the muscles of the Eustachian tube and of the tympanum. Only in rare instances are the changes in the intratympanic cavity so great as to cause permanent deafness. This is not so likely to happen in diphtheria as in scarlet fever.

Eyes.—Diphtheritic involvement of the conjunctiva is not very frequently seen. It occurs sometimes, but the wonder is that it is not more common in children, since they so often convey the infectious discharges from the nares to their eyes by means of their hands. Physicians and nurses who work among diphtheria patients are frequently subjected to the risk of infection by having the secretions from the throats of such patients coughed into their eyes. While we have sometimes seen a mild conjunctivitis occur from this accident, we have never known it to assume a diphtheritic character, though such a result is not impossible.

It has been suggested by some writers that the diphtheritic inflammation may extend to the conjunctiva by way of the tear duct, but this we believe is of rare occurrence. As an unhealthy mucous membrane is more prone to diphtherial infection, it is therefore probable that an acute or chronic inflammation of the eyes furnishes a predisposition to eye involvement when diphtheria occurs in a child thus afflicted.

When the conjunctiva becomes involved the membrane usually spreads rapidly from one eyelid to the other, and the bulbar conjunctiva is almost always greatly chemosed. The exudate is first seen as flocculi, but it rapidly forms into a thick membrane, so thick, indeed, as to press hard upon the cornea, causing it to become hazy and often undergo a destructive necrosis. When the cornea of the eye becomes weakened or perforated by this process the iris prolapses. During the

FIG. 130.—Diphtheritic involvement of the mucous membrane of the eyelids, showing, thick copious exudate on the inner surfaces of the lids, edema of the face and swelling of the glands of the neck. Vision was destroyed and death ensued.

course of the disease the eyelids swell and stiffen, so that it is almost impossible to inspect the eye itself. From what has been said it is evident that loss of vision is imminent.

Fortunately the affection is not always so destructive. In the milder cases recovery may take place without impairment of vision. But when the disease is so severe as to cause the destruction of both eyes, the patient's life is placed in great jeopardy. All such cases that have come under our observation have died.

Skin.—The diphtheritic membrane may appear on abraded surfaces of the skin, but this is by no means so common, even in the worst forms of diphtheria, as has been supposed. It is only in the wound of the skin from the operation of tracheotomy that this condition occurs with any degree of frequency. But even here the diphtheritic membrane

appears less often than one would suppose. We have, however, known the membrane to appear on the prepuce of a child who developed diphtheria immediately after circumcision, and Kolmer[1] has reported 2 cases along with a study of the diphtheroid bacilli occurring on the penis.

Warren and Sutton[2] have recorded a fatal case of diphtheria of the skin, and Roberts[3] a case of diphtheria developing at the site of a blister on the big toe which promptly recovered after the administration of antitoxin. Landau[4] found 18.2 per cent of 170 wounds carrying diphtheria-like bacilli but none of which proved typical virulent organsisms.

Some writers describe a rash that is sometimes seen as the result of diphtheria. It is said that it may appear at an early stage of the disease and that it is erythematous in character. It is described as either localized and evanescent, being scarcely visible for more than a few hours, or as covering a large surface of the skin and remaining for some days. We must confess that we are not familiar with any rash that can be said to be pathognomonic of diphtheria. When a circumscribed or diffuse rash of punctiform character is present, one should think of scarlatinal infection, for scarlet fever and diphtheria not infrequently coexist. The former disease cannot necessarily be excluded because the body temperature is low. Over and over again we have seen these diseases coexist when the temperature was but little above normal.

Edema.—Edema of the face and some other parts of the body is sometimes seen as the result of intense systemic poisoning, and quite independent of disease of the kidneys.

In the worst forms of diphtheria it is not uncommon to find petechiæ, purpuric discolorations and ecchymoses. The latter may occur spontaneously or result from the slightest bruise.

Antitoxin rashes, so common since this agent has come into use, are postponed for consideration under the head of the antitoxin treatment of diphtheria.

Toxemia.—A peculiar train of symptoms often results from absorption of the toxin elaborated by the specific organisms of diphtheria. These symptoms are so peculiar that one who is at all familiar with them would seldom fail to associate them with diphtheria, even in the absence of any other clinical manifestations of this disease. They often follow the disappearance at a time when the physician may feel that his patient is on the straight road to recovery.

When symptoms of toxemia occur they usually make their appearance during the second week of the illness. They may, however, be seen a little earlier or a little later. Frequently about the time the exudate has disappeared the patient commences to vomit, and the stomach becomes so irritable that everything is ejected almost as soon

[1] Arch. Pediat., 1912, vol. **29**.
[2] Jour. Am. Med. Assn., 1925, **84**, 1983.
[3] Lancet, 1923, ii, 785.
[4] Klin. Wchnschr., 1923, **2**, 595.

as swallowed. Pallor at once is noticed, and this rapidly increases, giving the face a remarkably blanched appearance. The change of color to a pale, waxy hue is sometimes so sudden as to come in the nature of a surprise. Coincidently with these symptoms the pulse becomes weak and often irregular. It may be either slow or rapid. The force of the apex beat of the heart is diminished, and the first sound indistinct. As the case progresses, the pulse becomes weaker and slower, often not more than 40 to 50 per minute. The extremities are cold. The mind is clear, but the patient shows an anxious expression. Albumin is most always found in the urine. The temperature is apt to be low, often, indeed, subnormal.

When toxemia is not profound the symptoms may gradually improve and recovery follows. But the condition of the patient should always be regarded as extremely critical. Often the signs of improvement are more apparent than real. For example, a patient may be entirely conscious, converse intelligently, sit up in bed and take nourishment, and, despite this apparent improvement, fall over and die almost instantly of heart failure. More frequently, however, death comes gradually, and is almost invariably preceded by precordial pain. The heart sounds become less and less distinct, and the pulse grows more and more feeble until it is absolutely lost. It is not rare for a patient to live for hours, sometimes even a day or two, with no perceptible pulse at the wrist. It is remarkable to note that consciousness in this condition is usually retained to the last.

Septic Diphtheria.—In diphtheria there are always associated with the specific microörganisms streptococci and staphylococci in great abundance, and the latter often give rise to a concurrent septic infection which constitutes an important factor in the course of the disease. It is sometimes difficult to determine to what extent this secondary infection is responsible for results, as distinguished from those of the primary infection. Doubtless in many cases of diphtheria streptococcus infection is the principal cause of death.

Septic infection is most liable to occur in patients with intense nasal involvement, and in whose fauces the exudate assumes a dirty-gray or brownish appearance. Instead of becoming detached and peeling off *en masse*, the exudate breaks down into a semi-solid or grumous mass. In such cases the decomposing and liquefying membrane gives rise to an offensive discharge from the nares and mouth, and a fetid breath. This discharge, ichorous in character, causes reddening and excoriation at the orifices of the nose and corners of the mouth, and the denuded surfaces are often converted into ulcers which quickly take on a dirty-gray coating. Sometimes there is considerable ulcerative action seen in the fauces and nares, but, strange to say, this process is commonly limited to the mucous membrane. It is only in rare cases that the subepithelial tissue is lost to a greater extent than would result from a small ulcer here and there. These ulcers are apt to remain covered for a long time with a yellowish coating.

The disorganization of the mucous membrane of the affected parts is commonly attended with capillary hemorrhages, more or less marked.

As might be supposed, the color of the false membrane is changed by its becoming infiltrated with blood. When the hemorrhages are copious, and the blood is poured out between the mucous membrane and the exudate, the latter is quite sure to be separated to a considerable extent. It is, therefore, not unusual to find in such cases a good deal of loose exudate in the throat, and in the nose also, undergoing rapid decomposition.

As the result of septic infection, the lymph glands of the neck become inflamed and swollen. The periglandular connective tissue may also inflame and swell to a certain degree. In some cases the swelling is so great that the neck is raised to an even line with the face. The skin becomes tense, smooth and shining, and may either feel doughy to the touch or as dense as a board. Suppuration may or may not result.

Attention has already been called to the fact that in septic cases a rash is apt to appear on the skin. The rash may at first be erythematous or slightly macular, but as the disease progresses it often assumes a petechial character.

In this form of diphtheria the temperature runs comparatively high, ranging from 102° to 104° F. There is usually considerable variation between the morning and evening records. The pulse is rapid and feeble, and the extremities are often cool. Suppuration of the middle ear is liable to occur, and pneumonia sometimes develops.

Children, restless at first, become apathetic later on, which condition increases until death supervenes. Death, however, is not the inevitable result, for the milder cases frequently recover.

Fever.—Except at the onset of diphtheria, fever is not a prominent symptom. The disease almost always begins with fever, more or less intense. In the milder cases the temperature of the body may not rise much above the normal, but in the severer cases, during the first day or two of the disease, it usually ranges from 101° to 102° F.; but after the full appearance of the exudate, that is, after the second or third day, the temperature commonly drops to normal, and sometimes below. Our experience accords with that of Lennox Browne, who says: "Of 1000 cases which came under observation, on an average, on the third day of the diphtherial attack the temperature in 80 per cent was 101° F., while in 50 per cent the average temperature during its course was below 99° F."

As already stated, the average temperature in the septic form of diphtheria is always comparatively high, while in the toxemic cases it falls to normal and even lower.

In acute adenitis, which often occurs as a complication in diphtheria, the temperature ranges high, sometimes to the extent of 104° to 106° F. If suppuration takes place and the pus is liberated the hyperpyrexia at once subsides. In every case of continued high temperature one should suspect the existence of some complication. The degree of

fever under such a circumstance is usually not different from that which is characteristic of the associated disease.

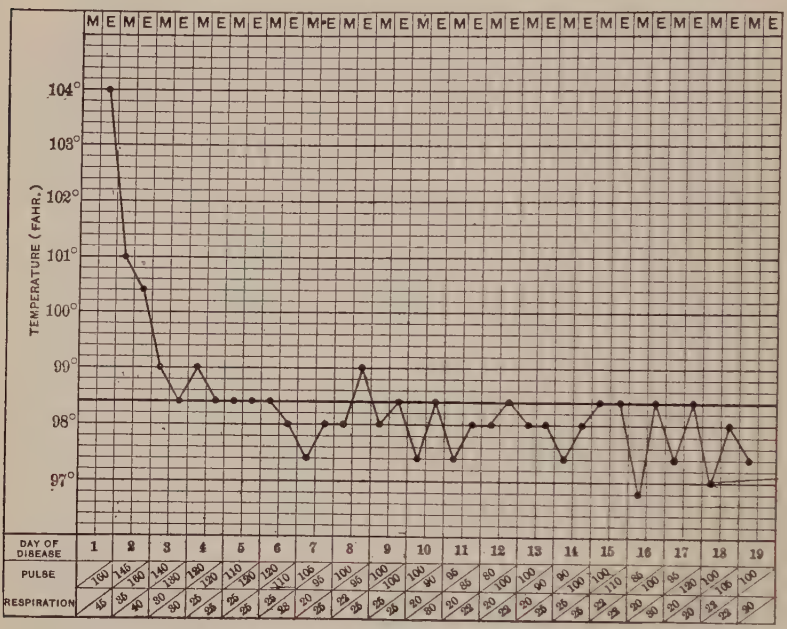


FIG. 131.—B. G., ordinary type of diphtheria, occurring in a child aged five years, showing a high initial temperature with a rapid decline.

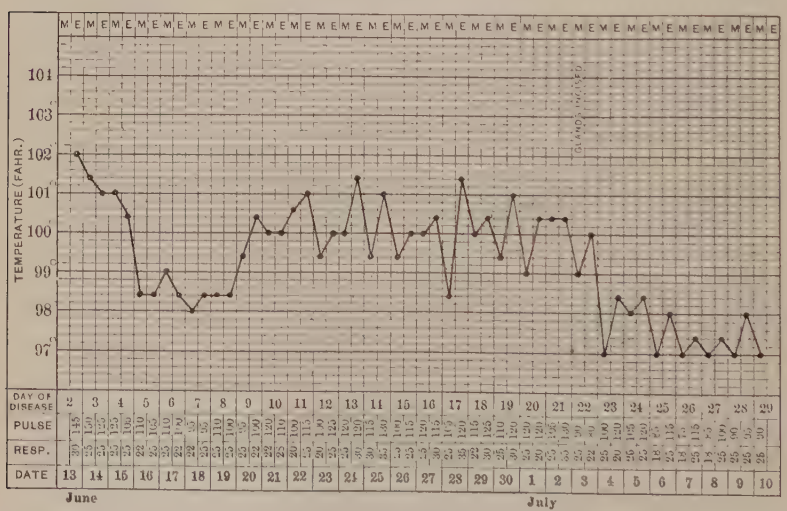


FIG. 132.—E. M., aged five and a half years; septic type of diphtheria in a patient with copious exudate in the throat; swollen cervical glands, later suppurating. Recovery.

What has been said of the temperature in ordinary diphtheria does not apply with equal force to the laryngeal form of the disease. In this class of cases, instead of falling after the first two or three days

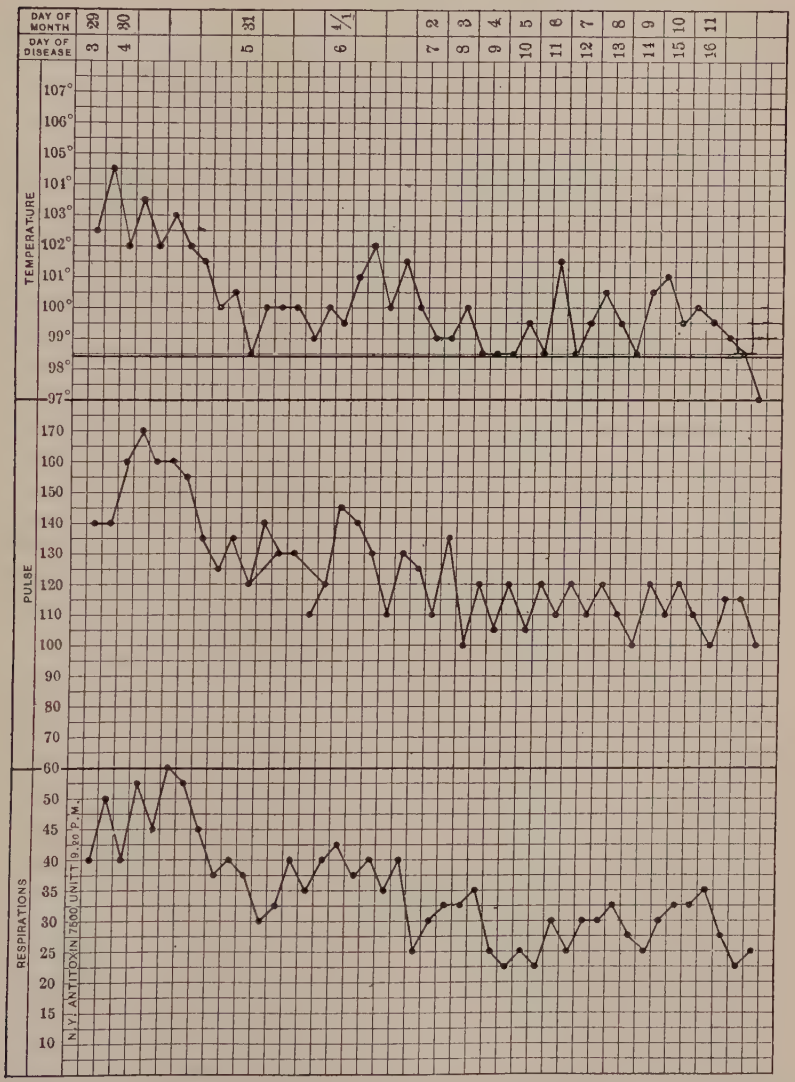


FIG. 133.—C. S., case of laryngeal diphtheria of average severity admitted on the third day of the disease, showing decline of temperature after removal of the intubation tube. Recovery.

of illness, it frequently continues high, especially when intubation is required for relief of the stenosis, and while the tube is in the larynx. In the majority of such cases the temperature continues to 101° to

102° F. for a number of days. If bronchopneumonia develops, which is not an infrequent complication, the temperature will continue high for an uncertain length of time.

The Heart and Circulatory Symptoms. —In all well-marked cases of diphtheria the pulse is frequent. Its rapidity, indeed, may be out of proportion to the temperature. In severe cases, especially in children, the pulse ranges between 120 and 160 per minute, and, as the disease progresses, becomes irregular and weak. The apex beat of the heart is often diminished in intensity and the first sound becomes indistinct. Attention has already been called to the fact that the action of the heart is greatly influenced by the profound asthenia resulting from toxemia. An abnormally slow pulse is of grave import, and will be referred to again when considering the question of prognosis.

It is generally recognized by clinicians that the heart is involved in many cases of diphtheria. Irregularities of various sorts may be observed; and since the development of electro-cardiographic methods of observation, almost every type of arrhythmia has been reported in connection with this disease, in which cardiac failure is an outstanding cause of death. Marvin,[1] for example, has reported disturbances in auriculo-ventricular or intraventricular conduction as the chief changes in a study of 90 cases; Marvin and Buckley[2] also report 2 cases of complete heart-block in addition to 9 proved cases collected from the literature. Hoskin[3] reports the occurrence of tachycardia, sinus arrythmia, enlargements, altered heart sounds, etc., and believes that the effect of diphtheria toxin on the heart, in those cases in which it has become involved, is more lasting than is generally recognized.

Great uncertainty exists, however, regarding the nature of the processes that involve the circulation so seriously in such circumstances. An extensive literature has accumulated in which it seems to be debated whether the cardiac failure is attributable to injury and deterioration of the myocardium or its conducting system, or whether the disturbance rather is extracardiac, involving the peripheral vasomotor system. Mere bedside observation cannot furnish a complete and satisfactory answer to the questions at issue. The subject is one that demands for its proper elucidation that combination of careful clinical study of the patient, along with detailed postmortem examinations in the cases with fatal termination, which represents the highest type of medical investigation. A recent report by Loth[4] on the heart in diphtheria represents a study of this kind in which death was found to be due to circulatory failure referable to injury of the myocardium itself or its conducting system. MacCallum,[5] however, in an experimental study, found that the actual work of the heart poisoned by diphtheria was fully as good as that of the normal heart. Consequently, he concluded that death occurring at the height of an attack

[1] Am. Jour. Dis. Child., 1925, **29**, 433.
[2] Heart, 1924, **11**, 309.
[3] Lancet, 1926, ii, 1141.
[4] Arch. Int. Med., 1923, **31**, 637.
[5] Am. Jour. Med. Sci., 1914, **147**, 37.

of the disease is not exclusively the result of direct injury to the heart, although damage to this organ may play some part in the process. Loth has observed that the injection of lethal or sublethal doses of diphtheria toxin in guinea-pigs produces degenerative changes in the heart muscle similar to those seen in the human heart in fatal diphtheria; but such injections do not induce a true inflammatory reaction. In the human cases a definite myocarditis of this sort is only exceptionally demonstrable at necropsy. Fat accumulation and cloudy swelling are regularly seen, but are not more pronounced than in other acute infectious diseases, such as scarlet fever, measles and pneumonia. In a study of hearts from 16 necropsied cases of diphtheria, Warthin[1] found that the essential lesion was a toxic parenchymatous hyaline degeneration or necrosis, associated frequently with fatty degenerative infiltration and less frequently with cloudy swelling or a simple necrosis. Either a complete regeneration or a fibrosis may result. The toxin of diphtheria may damage the conducting mechanism as well as the contractile, but no especial affinity is shown pathologically for either apparatus.

The Urine.—In the milder cases no marked change is found in the urine, either in the quantity voided or its constituents. In severe cases it contains an excess of urea, and sometimes epithelial cells and casts. Hematuria is much less common than in scarlet fever. Albumin in small quantities is found in a large proportion of cases. It is said to be present in about one-third of all cases; but this estimate is, according to our experience, much too low. Some writers believe that albumin is more often found since antitoxin has come into use. Suppression of urine and uremic symptoms are rare. This subject will be referred to again when considering the complications of diphtheria.

Nervous Symptoms.—In the acute stage of diphtheria nervous symptoms are not a prominent feature of the disease. Convulsions sometimes occur as an initial symptom in children of nervous temperament. In fatal cases convulsive movements are not infrequent in the death struggle. Delirium occurs only in exceptional instances, and when present is usually mild. Children, as a rule, sleep well; they often, indeed, lapse into a state of apathy or stupor.

Paralysis of the palate is often seen during the acute stage, or, at least, before the exudate has entirely disappeared from the fauces. We have frequently noticed its presence as early as the seventh to the tenth day of the diphtherial attack. Its existence is manifested by slight difficulty in deglutition, and by a nasal tone of the voice. Also, at an early stage of the disease the cardiac nerves may become involved, giving rise to cardiac syncope, which is a common cause of sudden death. General paralysis frequently occurs during convalescence. This will receive due consideration under the head of sequelæ.

Laryngo-tracheal Diphtheria, or Membranous Croup.—This form of diphtheria may be described as a pseudo-membranous exudation into

[1] Jour. Infect. Dis., 1924, **35**, 32.

the larynx and trachea, giving rise to symptoms of croup. It owes its origin to the same specific cause that is operative in producing diphtheria of the fauces and nares, namely, the Klebs-Loeffler bacillus. Before this organism was discovered and definitely shown to be the material etiological factor of diphtheria exudation, it was pardonable to have considered membranous croup as the result of a non-specific laryngo-tracheal inflammation. It is certainly no longer permissible to speak of an idiopathic catarrhal croup, except as applied to a spasmodic affection of the larynx of an entirely different character. Catarrhal croup is quite free from danger and non-contagious.

It must be admitted, however, that pseudo-membrane may form in the larynx, as on the tonsils, from microbic causes in which the Klebs-Loeffler bacilli have no part. The streptococcus is the particular microorganism found in this condition, and is believed to be responsible for the membrane, although the staphylococcus has been found as well. The symptoms caused by an exudation in the larynx due to these organisms are precisely the same as those caused by the genuine bacillary exudation. If differentiation be possible, it is only by the aid of bacteriological examination.

Our experience leads us to believe that an exudation into the larynx and trachea of streptococcic origin is uncommon. While admitting the possibility of such an occurrence, it is certainly safer, both for the patient and the public to regard and treat all cases of membranous croup as genuine diphtheria.

Some authors teach that in diphtheria the exudation rarely occurs primarily in the larynx and trachea, believing that it invades these parts by downward extension. This is undoubtedly true of most cases, but we have frequently seen membranous croup in children whose fauces and nares were entirely free from membrane. Some of the worst cases are of this description. Our experience warrants the statement that in fully one-half of all cases there is only scanty exudation in the fauces. It is often seen only on the tonsils in the form of dots, but may present a scattered appearance on the adjacent parts. In many instances the exudation will be found at the outskirts of the larynx on the lateral glosso-epiglottic folds. The epiglottis is frequently involved. Lennox Browne believes that the epiglottis is almost invariably first attacked, and seldom escapes. His experience leads him to believe that it is the rule, when the larynx is involved, for the exudation to begin on some parts of the fauces and extend downward.

While laryngeal symptoms often constitute the first evidence of diphtheria in children, there are many instances of the disease beginning in the fauces and nares and continuing for several days in a severe form before the larynx becomes involved. This has been called descending diphtheria. In this, and, indeed, every form of the disease, the exudation may extend into the trachea, the bronchi and even into the bronchioles (Fig. 134). Bly[1] has recently reported a fatal case

[1] Jour. Am. Med. Assn., 1926, **86**, 1833.

in a woman, aged thirty-four years, who coughed out a large piece of membrane which proved to be a cast of the trachea, both bronchi and several bronchioles.

Cases of ascending croup have been described; that is to say, the exudation beginning in the bronchi has extended upward into the trachea and larynx. This cannot be proved, and it is doubtful whether it ever occurs.

FIG. 134.—A cast of exudate expelled from the upper air passages by coughing. The cast extended from the larynx downward into the subdivisions of the right and left bronchi.

Symptoms.—When diphtheria exudation invades the larynx the symptoms vary somewhat according to the age of the patient. In children, in whom the lumen of the larynx is small, symptoms of impaired breathing soon appear. The symptomatology may be divided into three stages, according to the development of the disease. In the first stage the symptoms consist of cough and hoarseness, in the second of aphonia and dyspnea, and in the third of suffocation and asphyxia, speedily ending in death if relief be not afforded. It must

not be supposed that all three stages are seen in every case, for there are undoubtedly instances of abortive croup.

When the larynx is primarily attacked the disease at first is often thought to be nothing more than a common cold; but as it progresses its real nature becomes apparent. There is always cough, more or less pronounced, and it soon becomes hoarse and high-pitched, with a shrill, metallic sound. Hoarseness and huskiness of the voice exist with some discomfort in the throat and moderate fever. As the exudation increases the voice becomes less and less distinct, and often loses its sonorous character. Frequently, at an early stage of the disease the symptoms do not prevent the child from getting out of bed and playing, even when there may be some evidence of beginning dyspnea. In one, two or three days marked disturbance of the respiration is noticed, often sufficient to cause grave apprehension. The obstruction of the larynx, due to exudation and swelling, is sometimes increased by spasm of the laryngeal muscles. As the disease advances respiration becomes more and more difficult, until distressing dyspnea supervenes. The inspired air is insufficient to fully expand the lungs, which is evident from the sinking in of the lower end of the sternum and the lower ribs at each act of inspiration. The blood is insufficiently oxygenated, as denoted by a livid hue of the skin. The child is restless, cannot sleep, constantly changes its position in bed and vainly looks in every direction for relief. One does not often see a more pitiable sight than a little child suffering from well-developed membranous croup.

Laryngeal diphtheria is by far less common in adolescent and adult persons, and much less fatal, because the danger from stenosis is not so great. The greater development of the larynx in persons of mature years permits of some diminution of its aperture without affecting seriously the respiratory act. We have, however, met with a few instances in which the mechanical obstruction was so great as to demand operative interference. When the exudation is limited to the larynx intubation will afford relief, but when the trachea is also involved tracheotomy is to be preferred.

In membranous croup the temperature is usually higher than in faucial diphtheria. While the intubation tube is being worn the temperature is liable to remain 2° or 3° F. above the normal.

The laryngo-tracheal form of diphtheria has a decidedly local character, and is, therefore, not so liable to be attended with symptoms of systemic poisoning. Toxemia and general paralysis are not often seen in this form of the disease when it is strictly localized. The infrequency of constitutional symptoms may be accounted for by the comparative absence or scantiness of lymphatics in the larynx and trachea. Apart from the stenosis, the principal source of danger in membranous croup is from capillary bronchitis or bronchopneumonia.

THE COURSE, DURATION AND TERMINATION OF DIPHTHERIA.

In *mild cases* of diphtheria the local lesions are moderate in degree and the constitutional symptoms not serious. The exudation is scanty and limited to the tonsils. At the onset the temperature usually rises 2° or 3° F., sometimes a little higher, but quickly falls to near the normal. The mucous membrane of the fauces is congested, and deglutition slightly painful. There is usually loss of appetite and some prostration. The pulse-rate is accelerated—the rapidity at times being out of proportion to the rise of temperature.

In this purely local form of the disease the height is reached in from two to four days, when all the symptoms begin to subside. The exudation disappears, and the small areas of superficial ulceration left behind rapidly heal. In from four to seven days the fauces assume their normal appearance, and the patient expresses himself as feeling well, although there is apt to be some loss of strength and anemia. Sequelæ are extremely rare.

In the *severe type* of diphtheria the constitutional symptoms are usually well marked from the beginning. The temperature runs up quickly to 102° or 103° F., there is loss of appetite, the throat is painful and the child is restless and unable to sleep long at a time. Chilly sensations may be experienced and occasionally convulsions occur.

When an early examination of the throat is made the mucous membrane will be found to be of a vivid-red color, with moderate swelling of the parts. The uvula soon becomes edematous, elongated and swollen. This inflammatory action does not continue long, perhaps only a few hours, until the exudate appears. In its earliest manifestation it presents the form of grayish or yellowish-white spots of pin-head size. These form into groups which quickly coalesce, and thus develop into large patches. In most cases the exudation is first seen on the tonsils and rapidly spread to other parts of the fauces. Frequently, in twenty-four to forty-eight hours it covers not only the tonsils, but the anterior pillars, the uvula and a large part of the soft palate. With this increase of exudation the temperature, strange to say, often falls 1° or 2° F. The lymphatic glands of the neck, near the angle of the jaw, are almost always swollen.

In *favorable cases* the local symptoms reach their maximum development in forty-eight hours, and after remaining stationary for a day or two begins to subside. The exudation sometimes exfoliates in large masses and at other times melts away little by little. When it becomes detached and peels off it may disappear entirely in from six to eight days, sometimes sooner; but when it melts away gradually a longer time is required. The mucous membrane of the parts involved is left reddened and shows superficial ulceration. Often the uvula suffers the greatest loss of substance from the ulcerative action, as it is honeycombed, shrivelled and tapers down to a small point. The ulcers usually heal rapidly. Simultaneously with the decrease of exudate the

pulse becomes less frequent, and in favorable cases maintains fair volume and regularity. The swelling of the glands of the neck subsides, the appetite improves and the patient is fairly on the road of convalescence. But even when recovery seems most probable the physician in giving a prognosis should express himself with some reservation, for dangerous symptoms may yet follow, such as indicate toxemia, heart failure or paralysis.

In *very severe cases* all symptoms are, of course, greatly intensified, and complications are much more liable to ensue. The exudation is usually copious, covering thickly the entire fauces, and is often seen extending forward on the vault of the mouth beyond the junction of the soft and hard palates, on which location it is apt to be especially thick

It frequently travels backward to the pharyngeal wall, the postnasal space and into the nares. It may even extend downward into the larynx and trachea.

As already mentioned, the local and constitutional symptoms do not progress *pari passu*. On the contrary, while the exudation is increasing the fever may diminish to such an extent that the body temperature is but little above the normal. The pulse-rate, however, does not always decrease proportionately, but may even grow more rapid. The appetite often improves, swallowing appears to be less painful and not infrequently the general condition and strength of the patient seem improved, while the danger is in nowise diminished. The physician should be careful not to be misled by this apparent improvement while the disease is still progressing.

When diphtheria assumes the *septic form* the secretion and exudation of the throat and nares undergo rapid decomposition, and, unless these parts are frequently cleansed with antiseptic washes, there is emitted with the breath a peculiar odor which is in the highest degree offensive. This odor is often so foul as to suggest the existence of gangrenous destruction of the tissues, and yet the disorganization of the parts rarely amounts to more than a superficial ulceration. Coincidently with this condition, the cervical and submaxillary glands, usually somewhat swollen from the beginning, greatly increase in size by inflammatory action, which also involves the adjacent cellular tissue. While abscesses frequently form, yet it is surprising how rapidly this swelling will often subside without abscess formation as soon as the throat symptoms show signs of improvement.

In *septic cases* the fever, instead of diminishing in two or three days, as in the other varieties of diphtheria, continues, or may even increase, until the throat and nose symptoms improve and the swelling of the neck subsides. Recovery may take place from this form of the disease, but the majority of patients die. Death often occurs at an early stage, as early as the fifth to the seventh day, from extensive systemic poisoning due to a mixed infection. Sometimes the poisoning is more gradual, in which case the exudate disappears, the glandular swelling subsides

and the temperature falls, but instead of improving the patient remains apathetic, loses weight, becomes anemic, grows weaker and weaker and gradually passes away. A not uncommon cause of death is pneumonia of septic origin.

The presence of epithelial and hyaline casts in the urine, together with a large amount of albumin, points to a rapidly developing systemic poisoning, and may often prove to be an early monitor of danger.

When recovery takes place from the septic form of diphtheria convalescence is usually very slow, often, indeed, extending through many weeks. The symptoms of septicemia become less and less marked, and prostration gradually gives way to general improvement. But in the fourth or fifth week of the disease, even after an apparent recovery, some late complication, more especially general paralysis, is extremely liable to set in. This is true not only of the septic form, but of all well-marked cases of diphtheria. The vast majority of patients recover from the paralysis, but it is sure to prolong the period of convalescence for weeks or even months.

In the *malignant type* of diphtheria the earliest symptoms give marked evidence of systemic poisoning. By the time the false membrane has formed, which is usually in twenty-four to forty-eight hours, the whole organism is profoundly affected. The membrane covers thickly the entire fauces, often involving the nares also; the breath is fetid, the saliva dribbles from the mouth, blood oozes from the nose and purpuric or petechial spots appear upon the skin; the glands of the neck and the periglandular tissue are greatly swollen; the face is bloated, pale and waxy in color; the temperature is either slightly elevated or subnormal; the pulse may be rapid and feeble or slow and irregular, and the intellect, clear at first, soon becomes clouded. Death in these cases may occur in forty-eight hours, and is rarely delayed longer than three or four days.

The course and duration of *membranous croup* vary in different cases, according to the extent of the disease. In mild cases the symptoms often disappear in a few days under ordinary treatment, without operative interference. When the larynx is involved to the extent of causing stenosis death is sure to result speedily if relief be not afforded. If the exudation is limited to the larynx the obstruction to respiration is almost always overcome by intubation, and in the course of six or eight days the patient may be considered comparatively free from danger, at least so far as the primary trouble is concerned. But when the exudation extends into the trachea, intubation may give relief at first, though death is liable to occur a few hours later. Death commonly results when the disease extends into the bronchi and bronchioles. It occurs through insufficient decarbonization of the blood, due to the mechanical obstruction caused by the false membrane and retained secretions in these parts.

In cases which linger longer the fatal result may be brought on by collapse of certain parts of the lungs to which the air does not have

access, or by the development of capillary bronchitis or bronchopneumonia. Many patients develop the latter affection when they are believed to be well on the way to convalescence. This, indeed, is one of the principal causes of fatal termination in laryngo-tracheal diphtheria.

When membranous croup is likely to terminate in recovery improvement begins with a decrease in the fever and an abatement of the laryngeal symptoms. The false membrane usually disappears in from four to eight days. Sometimes it is coughed up in cylindrical or irregular casts, but more often it disappears gradually, probably by being liquefied and expectorated; it is quite impossible to believe that it ever undergoes absorption. When thrown off in casts it is liable to reform, and when such new formations take place the disease is apt to terminate fatally. In patients that recover hoarseness or aphonia, and often some difficulty in swallowing, continue for a longer or shorter time after the intubation tube has been removed. This change in the voice, according to Oertel, is to be ascribed to a flaccid condition of the vocal cords and atony of the laryngeal muscles.

RECURRENCE OF DIPHTHERIA.

Many authors believe that a second attack of diphtheria seldom occurs in the same individual within a short space of time. While this may be accepted as the rule, yet it must be admitted that there are many exceptions. It is certainly true that a person who has survived the disease does not have conferred upon him for any considerable length of time that immunity which is so characteristic of scarlet fever, measles and smallpox.

We have quite often readmitted children to the hospital with recurrent diphtheria within a few months from the previous attack; and in 2 or 3 instances, at least, children have returned with a third attack. Quite often also have we seen patients suffer from a relapse of the disease before leaving the hospital. In such instances, after the subsidence of all constitutional symptoms and the complete disappearance of the membrane, the patient, during convalescence, is seized with a sore throat, the temperature rises, the glands of the neck become swollen and sensitive, and the exudation recurs in the throat, or nares, or both.

The relapse is not, as a rule, so severe as the primary attack, but there are some exceptions. We have more than once seen death result from a recurrence of the disease.

COMPLICATIONS AND SEQUELÆ OF DIPHTHERIA.

Heart. -The poison elaborated by the bacilli of diphtheria is especially prone to affect the heart, and the subject has been previously discussed on page 644. In all severe cases heart failure is extremely

liable to occur. Symptoms of this condition may appear before the pseudo-membrane has entirely separated, but in most cases they are not apparent, or, at least, do not become prominent, until the characteristic feature of the local affection has, to a great extent, disappeared. In other words, signs of cardiac failure are rarely seen until the diphtherial process has made considerable progress. They do not often appear before the end of the first week, but during the four or five succeeding weeks the patient is in constant danger of heart failure.

It is believed by some authors that the heart is affected to a greater or less degree in all cases of diphtheria. Jacobi[1] says: "There is no case ever so mild apprently that will not affect the heart's function at once to a certain extent. From mild cases to the gravest there are gradual transitions." In a large proportion of the severe cases which survive long enough the myocardium shows (postmortem) certain anatomical changes, the most common of which is fatty degeneration.

The *symptoms of heart failure* do not differ from those of toxemia. Vomiting is often an early sign. The patient is pale and sallow, sometimes livid and cyanotic; the pulse at first may be rapid and feeble, but soon becomes slow, irregular and intermittent or dicrotic. The pulse-rate is frequently as slow as 40 to 50 per minute. The first sound of the heart grows less distinct. The circulation is sluggish and the extremities are cold, but the mind remains clear. In severe cases, as the end approaches, the pulse becomes absolutely lost at the wrist, and death results gradually from asthenia, or it may result suddenly from heart failure. Undoubtedly death sometimes occurs from paralyses of the cardiac plexus. Recovery but seldom takes place after the symptoms of heart failure once assume a threatening character.

Lungs.—In faucial diphtheria the lungs do not very often become affected. Bronchitis occasionally occurs, as does also bronchopneumonia. But in the laryngo-tracheal form of the disease these complications are extremely common. Indeed, bronchitis, more or less marked, is not very often absent in membranous croup. As the inflammation extends downward from the laryngo-tracheal surface to the bronchi, the inflamed mucous membrane is apt to become involved in the diphtherial process. But quite apart from this, bronchopneumonia, catarrhal in character, is of frequent occurrence, and constitutes one of the principal sources of danger. It most often sets in before the acute stage of membranous croup has passed, but it may occur at any period following this stage, even during convalescence.

When it develops at a later stage, or during convalescence, it is in most cases preceded by a mild bronchitis that has never entirely disappeared.

The existence of a bronchopneumonia is revealed by physical examination. Both lungs may be found involved, although the disease is usually better marked in one than in the other. The physical signs may show that the inflammation is limited to the lower lobes, but more

[1] Twentieth Century Practice of Medicine.

frequently disseminated areas of inflammation are found throughout one or both lungs.

As already stated, bronchopneumonia is one of the chief sources of danger in diphtheritic croup. The muco-purulent material secreted in the bronchial tubes may be so abundant as to clog the tubes and prevent proper decarbonization of the blood. As the inflammation extends to the smaller tubes, these often become clogged in the same way so as to prevent the entrance of air to the alveoli, which gradually collapse. Autopsies often reveal areas of atelectasis disseminated throughout the lungs. Even where the tubes remain pervious it is almost impossible for the child to expectorate the muco-pus on account of its viscidity. Hence, the minuter tubes are usually found (post-mortem) to be filled with a thick, viscid material, containing also not infrequently floating particles of pseudo-membrane.

Bronchopneumonia is always attended by an elevation of temperature. The disease may either run an acute course, terminating in recovery or death in six to eight days, or assume a subacute form and continue to progress for two, three or more weeks. In some of these persistent cases recovery finally takes place, but more often results from exhaustion. Bronchopneumonia is the chief cause of death after tracheotomy.

Lobar pneumonia is not a very frequent complication. It has been known to occur during the stage of convalescence. Areas of consolidation in the lungs are not infrequently seen, but they are almost always associated with inflammation of the bronchi.

Pleurisy does not very often occur as a complication. According to J. Lewis Smith, "Peter found the lesions of pleurisy 9 times in 121 autopsies in diphtheria, and Sanné observed them in 20 cases." The latter is quoted as saying that pleurisy always accompanies some other phlegmasia. In our experience in the hospital we have not seen more than 2 or 3 frank cases of pleurisy attended with pleuritic effusion.

Lymphatic Glands.—Enlargement of the cervical and submaxillary glands is of common occurrence in diphtheria. It may be either slight or excessive. In septic cases this complication is usually most marked. As already stated, the inflamed glands sometimes break down into abscesses.

Kidneys.—Renal complication occurs earlier in diphtheria than in scarlet fever. Albuminuria is frequently seen as early as the third or fourth day, sometimes even on the second, while the quantity of urine is not diminished, but may be increased. It is believed that the elimination of the toxin with the urine irritates the kidneys, and thus tends to affect their function or even damage their parenchymatous structure. In cases showing albuminuria the kidneys may be found to be normal, or they may exhibit various degrees of parenchymatous inflammation. While acute nephritis is not so common as in scarlet fever, yet it does occur. This is evident from the fact that hyaline and granular casts are sometimes found. Red blood cells are rarely present. The urine

in such cases is diminished, sometimes scanty, and the skin becomes pallid. Edema is less pronounced and uremic symptoms are much less frequent than in postscarlatinal nephritis. Still patients die now and then from uremia.

Scarlet Fever.—Scarlet fever is not an uncommon complication in diphtheria; or, more properly speaking, one of these diseases is often found associated with the other. We venture to say that anyone who has had experience in a hospital for contagious diseases will bear out this statement. Being familiar with the experience of, at least, two or three such hospitals, we know how frequently scarlatinal rashes are found in the diphtheria wards, and, on the other hand, how often diphtheria appears in the scarlet-fever wards.

In many cases of diphtheria with concurrent scarlet fever it is impossible to explain the source of the double infection. In hospitals for contagious diseases it is sometimes felt that one disease is engrafted upon the other through exposure to the second infection; but in private families these diseases not infrequently coexist without any known or explicable cause.

A function of a contagious disease hospital, second in importance only to the actual treatment of the disease for which a patient is admitted, is the prevention of mixed or crossed-infections. This function is often entirely overlooked except by those actually responsible for the welfare of the patient. Eighty-five per cent of the patients admitted into a hospital of this kind are under fifteen years of age, a time of life when they are most susceptible to the so-called diseases of childhood. Since these diseases are communicable, it can be understood that a general distribution or mixing of diseases is an easy matter, particularly when we recall that many cases are of the "border-line" variety, in which the diagnosis is not at all easy, and when many cases are admitted with one infectious disease, and at the same time in the incubation period of some other infectious disease. It is this danger or tendency to mix diseases in the old style hospital that has fastened on such institutions, even to this day, the stigma of pest house. As stated by Woody, the advancements made in recent years in efforts to control this most troublesome of all infectious-disease hospital problems has reduced this danger to a minimum unthought of even ten years ago.

Measles.—The relation of measles to diphtheria is a matter that has not received as much notice by writers as its importance deserves, and its occurrence with measles should be regarded with great apprehension, since the diphtheria is liable to assume the laryngo-tracheal form with the development of bronchopneumonia. But as stated on page 539, the intramuscular injection of children with the serum or whole blood of individuals who have had measles will almost always protect against the disease for several weeks, and since the introduction of this method at the Philadelphia Hospital for Contagious Diseases measles has ceased to be a serious problem.

Paralysis.—Paralysis might be regarded with much propriety as a symptom of diphtheria, but as it is not seen until the acute stage is passed, and more often during convalescence, we have preferred to consider it as a complication or sequela. Very little seems to have been known of diphtherial paralysis prior to the latter part of the sixteenth century. Nicholas Lepois called attention to it in 1580 and Miguel Heredia in 1690. According to J. Lewis Smith, Ghisi, of Italy, in describing an epidemic which occurred in 1747–1748, when his own son had paralysis in a severe form following diphtheria, says: "I left to Nature to cure the strange consequences . . . which had been remarked in many who had already recovered, and which had continued for about a month after recovery from the sore throat and abscess. During this period this child spoke through the nose, and food, particularly that which was least solid, returned through the nares in place of passing down the gullet." About the same time (in 1748) Chomel, of France, described 2 cases of paralysis following what he called gangrenous sore throat. In 1771 Dr. Samuel Bard, of New York, described the symptoms seen in a little girl, aged two and a half years, who had recovered from "Sore-throat Distemper," as follows: "Whenever she attempted to drink she was seized with a fit of coughing; yet she was able to swallow solid food without any difficulty. She improved, but in the second month she could scarcely walk or raise her voice above a whisper."

For the next fifty years and more but little is said of diphtheritic paralysis. This sequel must either have been overlooked or regarded as a coincidence, or else diphtheria at that time was of so mild a type that paralysis did not often result. It appears that Bretonneau had not yet observed this sequela at the time of his first publication on diphtheria in 1826. It is said by J. Lewis Smith[1] that Bretonneau "Did not recollect that he had seen a case of diphtheritic paralysis prior to 1843. Although a close observer of diphtheria, the paralysis had not been observed by him, or at least had not attracted his attention, until it occurred in the person of his townsman, Dr. Turpin, in 1843." From this time on, until his second publication appeared, in 1855, he saw a sufficient number of cases to convince him that this sequela occurs not infrequently, and called attention to it in his paper of the latter date. Since then nearly every writer on diphtheria has described this peculiar form of paralysis, and its frequent occurrence is an accepted fact.

Paralysis does not often follow mild tonsillar diphtheria. But when the soft palate and especially the nares are involved, partial or complete paralysis, not only of the muscles of the parts covered with exudate, but also of the entire muscular system is liable to occur. General paralysis does not appear immediately after the local evidence of diphtheria has disappeared, but develops gradually and slowly. The parts earliest

[1] Keating: Cyclopedia of the Disease of Children.

affected are the soft palate and the pharynx, while the upper and lower extremities show this symptom later. From the slow development of the affection it seems probable that at first only a few fasciculi are incapacitated, and that gradually more and more of these become involved until the affected muscles are no longer under the control of the will. Paralysis is sometimes observed in the muscles of the eyes, the trunk, the bladder, the rectum and the diaphragm. In most cases the paralysis is incomplete, but in rare instances it progresses to such an extent that the entire muscular system becomes incapacitated.

The cause and pathology of the paralyses are not fully understood. It seems probable that the condition is due to a toxic neuritis involving the peripheral nerves, causing an interruption of the nerve supply to the muscles involved. It is said that the neuritic change may extend the entire length of the nerves, from their periphery to their origin, not only of the spinal but also of the cranial nerves.

It may be that some of the fasciculi of the enervated muscles undergo fatty degeneration, as this change has been seen in the myocardium. Anatomical changes have been found in the spinal cord, apparently resulting from myelitis. S. G. Henschrn has reported a case of acute disseminated sclerosis of the cord and neuritis. Some writers believe that changes of this nature contribute an important part in the production of the paralysis. *Hemiplegia* is but rarely seen in diphtheria.

The frequency with which paralysis follows diphtheria depends upon the character of the epidemics, and the promptness with which antitoxin is given, since the early administration of large doses rapidly neutralizes the toxin and reduces the incidence. It occurs, of course, much more frequently in severe attacks than in mild attacks of the disease.

Since paralysis develops very gradually and slowly, it is not always easy to determine at which stage of diphtheria it begins. The difficulty is increased from the fact that most of the patients are young children in whom the affection is usually not discovered until the more characteristic symptoms have appeared. However, it has been found from careful observation that paralysis of certain muscles, the palatal, for example, may occur in the acute stage, or, at least, immediately after the disappearance of the pseudo-membrane. But the later manifestations, as seen in muscles remote from the fauces, especially in those of the extremities, diaphragm, etc., are more serious, and usually do not appear in a pronounced form until after an interval of more than four weeks from the commencement of the diphtherial attack.

While this sequela is not so often seen after the mildest attacks of diphtheria, at least not to any marked degree, yet instances have been recorded in which paralysis has occurred in persons who, presumably, were infected with diphtheria without having exhibited any of the ordinary symptoms of the disease.

The paralysis, as a rule, affects principally the motor nerves, although the sensory nerves are not infrequently involved also. Anesthesia of

some parts, particularly the fauces, has been observed, and tingling and numbness are sometimes felt in the extremities. The sense of taste has been known to be affected. Paralysis of the sensory nerves may be quite local, and is not seen until a somewhat later period than the motor paralysis.

As the symptoms and course of diphtheritic paralysis vary according to its location and muscles involved, it seems most convenient to speak of the clinical manifestations of its various forms separately.

Paralysis of the *palate* is often seen at an early stage of the disease. It may be observed as soon as the exudate has disappeared, or as early as the tenth day of the diphtherial attack. The first evidence is manifested by a nasal tone of the voice. This results from dropping of the soft palate, causing the air to escape through the nose in the act of speaking. There may be slight difficulty in swallowing, enough to make it necessary for the patient to drink cautiously. Later, in the third or fourth week, or after convalescence has actually set in, the deglutition may become more difficult, so that fluids, instead of being easily swallowed, regurgitate in large part through the nares, while some run down the larynx, causing cough and sometimes pneumonia. As already mentioned, *anesthesia* is associated with this form of paralysis and adds to the difficulty of swallowing. In infant starvation may occur through their inability to suckle. Even in older children, and in adults also, when general paralysis of an extreme form develops, deglutition often becomes impossible, and death from starvation may result if feeding through an esophageal tube be not resorted to.

When paralysis of the palate has continued for a week or two faulty accommodations of the *ocular* movements may be seen. Most frequently the paralysis of the ciliary muscles is bilateral. The most common variety of axis deviation met with is convergent strabismus, resulting from paralysis of the external recti muscles. *Diplopia is* not of infrequent occurrence.

Slight *facial paralysis* occasionally occurs. It has been noted as appearing soon after the acute stage. We have seen but very few such cases, and in these the affection was unilateral.

Paralysis of the *cardiac* and *respiratory nerves* may appear any time after the first week of the illness. The exudate may have disappeared, more food is taken, the patient appears to be gradually improving and the members of the family are cheerful at the prospect of a speedy recovery, when suddenly the scene changes. The heart action becomes weak, the pulse feeble, slow and irregular, sometimes rapid, the respirations superficial and the patient becomes pale, often slightly cyanotic. Severe precordial or epigastric pain is often complained of in cases of sudden heart failure. In the more favorable cases improvement may follow active stimulation, and the patient may eventually recover. But too often the improvement is only temporary, for the heart failure is liable to return after a few hours, or a day or two at the most, causing sudden and, to the inexperienced physician, unexpected death.

There is no other disease in which symptoms of heart failure occur so suddenly and unexpectedly, and there is perhaps no other disease in which physicians are so often deceived in the matter of prognosis.

Involvement of the *respiratory nerves* leads to paralysis of the diaphragm and sometimes pulmonary collapse.

General paralysis does not make its appearance until a very late stage of diphtheria. It is not often seen earlier than the fourth week, and may occur later than the sixth week. In most cases it appears between the fourth and sixth week. In almost every instance it is preceded by well-marked palatal paralysis, sometimes by loss of function of the muscles of the eye, especially those presiding over motion and accommodation. As a rule, the loss of power is first noticed in the lower extremities. This may increase until the limbs, especially the lower limbs, are rendered entirely useless for weeks.

The comparative immunity of the fingers in many cases may be mentioned as a peculiarity. Paresthesia or anesthesia, however, is frequently noticed in the fingers, palms of the hands and feet. The degree of paralysis is not the same in all muscles; in some it is complete, while in others it is only partial. When there is complete loss of power in the lower extremities it is not unusual to find that the patient has considerable use of the upper extremities. The muscles of the *trunk* are often partially paralyzed, but only rarely is there loss of sensation. In general paralysis the *diaphragm* is often affected, but rarely to the extent of seriously interfering with respiration. Its involvement is more apparent in the act of *coughing*. In this act, instead of the sudden expiratory explosion, the *cough* is slow and straining, and apparently attended with some effort on the part of the patient. But paralysis of the muscles of the pharynx, preventing complete closure of the glottis, may have more to do in causing this peculiar symptom than paralysis of the diaphragm.

As J. Lewis Smith very truly says, even where the paralysis seems to be general there are groups of muscles which entirely escape. He, therefore, prefers the term *multiple paralysis* to that of *general paralysis* to designate this form of the disease.

Of the internal and visceral muscles liable to become involved, paralysis of the *diaphragm* or of the *heart* is of the most serious import, as it may be responsible for sudden death. Alesen[1] has recently recorded the recovery of a case of bilateral diaphragmatic paralysis.

The *bladder* is sometimes involved, but rarely to any marked degree. We have never found it necessary to catheterize a patient to relieve this viscus, nor have we ever observed any loss of power in the sphincter muscles. Paralysis of the muscles of the *lower bowel* and *rectum* is said to occur at times, giving rise to constipation, but not affecting the sphincters.

Lastly *tendon reflex paralysis* is very common. Indeed, it is said to

[1] Jour. Am. Med. Assn., 1925, **84**, 730.

be the most frequent of all the paralyses, probably occurring in one-third to one-half of all well-marked cases of diphtheria. Hughlings Jackson called attention to the fact that loss of knee-jerk is usually one of the earliest symptoms of paralysis. Dr. R. L. McDonnell, of Canada, believes it is present in many cases of diphtheria from the very first day of the illness. It is not only the earliest of the paralytic symptoms to appear, but is also of longest duration. In many cases normal reflex returns after an interval of four to six months.

Regans and Wilson[1] found the *cerebrospinal fluid* is postdiphtheritic paralysis to be clear and limpid, flowing usually under normal or slight hypertension. The Wassermann reaction was uniformly negative in each of 16 cases. The cell count was always within normal limits, less than 10 cells per cubic millimeter, and the cells found were small lymphocytes. The globulin was increased in less than one-third of the cases. The increase was slight, occasionally moderate, never marked. There existed, therefore, in certain cases (less than one-third) a dissociation between the cytological and chemical findings. The colloidal-gold reaction was the most constantly positive pathological reaction encountered in the fluid of this disease. The reduction usually occurred in the syphilitic zone, occasionally extending into the higher dilutions. The reaction seemed gradually to subside, reaching normal as convalescence was established and paralysis disappeared.

The frequency of postdiphtheritic paralysis varies in different seasons, and, as already stated, in different epidemics. It has been found to occur in from 10 to 30 per cent of all cases of diphtheria. The affection is never permanent. Its duration is from two to six months, counting from the time it first appears until normal motion is restored in all muscles.

Non-diphtheritic Exudates (Pseudo-diphtheria).—The term pseudo- or false diphtheria is now commonly applied to an inflammatory affection of the throat characterized by the appearance of a peculiar exudation in which the Klebs-Loeffler bacillus is absent. It may occur primarily as a catarrhal inflammation of the fauces, in which case it is rarely severe, except when the larynx is involved; or it may occur secondarily in the course of some other affection, like scarlet fever or measles, when it is frequently fatal.

While pseudo-diphtheria is often seen associated with scarlet fever or measles, yet it must be remembered that true diphtheria not infrequently coexists with either of these diseases. Most writers believe that when pseudo-diphtheria occurs in the course of scarlet fever or measles it is more liable to appear at the height of the primary disease, while true diphtheria more often develops during convalescence. Our experience leads us to believe that this is true with reference to measles only.

It is now well known that pseudo-diphtheria is usually due to the Streptococcus pyogenes. This organism may be found alone in the

[1] Am. Jour. Dis. Child., 1923, **25**, 284.

exudation, but commonly the Staphylococcus aureus or albus is also present. It is said that the staphylococcus is occasionally the only organism found. The condition of the throat of persons suffering from scarlet fever, measles and perhaps some other infectious disease is favorable for the propagation of these germs. They are, indeed, often found when no exudation is present.

Woody and Kolmer[1] have reported 24 cases of Vincent's angina sent to the Philadelphia Hospital for Contagious Diseases in 1911 in mistake for diphtheria; also 74 cases of pneumococcus pharyngitis. Of 447 cases sent in with the diagnosis of diphtheria 5.59 per cent proved to be streptococcus and 3.35 per cent staphylococcus infections.

In streptococcus, pneumococcus and staphylococcus infections the disease makes its appearance like an ordinary sore throat. There may be vomiting, slight rigors, headache, general pains, painful deglutition and fever. The constitutional symptoms are usually well marked at the beginning. During the second or third day of the disease the temperature may rise to 103° to 104° F., but it quickly falls and the other symptoms also subside. On inspecting the throat the mucous membrane is found reddened and the tonsils swollen. Very soon an exudation appears upon the tonsils and sometimes upon other parts of the fauces and the buccal mucous membrane also. The exudate is grayish in color, shreddy or pultaceous and seems to lie upon the surface, as it may be readily removed with a cotton swab. It does not remain long, usually disappearing in three or four days. The inflammation of the throat is often more marked than in genuine diphtheria, and swelling of the lymphatic glands in the neck may be seen, though this is not excessive in mild cases.

In many cases of pseudo-diphtheria in which the disease is secondary to another affection the symptoms are as mild as those just described. But frequently the local manifestations are as severe as in the worst forms of pharyngeal diphtheria, and the constitutional symptoms as well marked as in the septic form of that disease. Indeed, the clinical description given of scarlatina anginosa by some of the older writers is not essentially different from that of septic diphtheria, at least so far as the greater part of the local and constitutional symptoms are concerned.

In scarlet fever the streptococcic process is liable to set in at an early stage of the disease. In severe cases the process may reach its maximum in the latter part of the first week, and continue for two weeks or longer. The disease almost always involves the nose as well as the fauces, and very frequently extends to the middle ear, giving rise to a suppurative otitis media, which may permanently affect the hearing.

When pseudo-diphtheria occurs secondary to measles the throat involvement is mild as compared with scarlet fever, but the streptococcic process much more frequently extends to the larynx, giving rise

[1] Arch. Pediat., 1911, **28**, No. 6.

to a dangerous form of membranous croup. When this condition develops there is not only danger from stenosis, but also from bronchopneumonia. Sometimes the larynx is involved when there is no sign of exudate in the fauces. Holt believes that this is very infrequent unless the disease is true diphtheria; but we have seen a number of such cases in which the Klebs-Loeffler bacillus was absent.

Vincent's angina is considered separately in Chapter XVIII.

From a clinical point of view it is often difficult to distinguish between these non-diphtheritic anginas and true diphtheria. We believe that in the majority of cases the experienced physician will make a correct diagnosis at the bedside, yet frequently one most skilled in the art of diagnosis will find it impossible to say, in a given case, that the pseudo-membranous affection of the throat is not true diphtheria. In such cases the assistance afforded by bacteriology is of great importance. Holt very truly remarks: "The bacteriologists have taught us to be cautious in pronouncing too positively upon even the mild cases, as it has been clearly shown that some of them may be caused by the most virulent of diphtheria bacilli."

Even in the secondary cases one should not be too ready to exclude true diphtheria in making the diagnosis, for it is well known, as has been already pointed out, that this disease often coexists with scarlet fever, and not infrequently follows in the wake of measles, particularly when it is prevailing in the neighborhood.

As pseudo-diphtheria is rarely communicated from one person to another, the enforcement of stringent preventive measures, such as quarantine and disinfection, does not seem to be necessary. It is, however, advisable to exclude healthy children from the sick-chamber. In regard to the secondary cases, especially when the primary disease was scarlet fever or measles the complicated cases should certainly be separated from the others.

The vast majority of primary cases require but little treatment. The patient should be put to bed and given a light diet. If the bowels are not regular a mild cathartic may be administered. Gargles are of service when the patient is old enough to use them properly. They may consist of almost any mild antiseptic solution. Boric acid in the proportion of 5 to 10 gr. to an ounce of water makes a useful gargle; so also does potassium chlorate in solution (teaspoonful to a glass of water). Instead of using gargles, the throat may be sprayed by means of an atomizer with the boric acid solution, or with hydrogen dioxide in the proportion of 1 to 2 or 3 parts of water. Internally, tinctura ferri chloridi in suitable doses will be found serviceable.

In the secondary cases closer watching is required, as regards both the local and constitutional symptoms. If the child is old enough, more active antiseptic gargles should be used, such as Dobell's solution, perhaps slightly diluted, or 1 to 5000 to 1 to 10,000 solution of bichloride of mercury, or hydrogen dioxide, diluted as mentioned above. The gargle should be used every hour or two during the day, but not quite so often through the night.

For accomplishing the purposes of a gargle, the atomizer will often be found more convenient and satisfactory. Dobell's solution, a 1 or 2 per cent solution of boric acid, or the hydrogen dioxide, will frequently give good results.

If the nares be involved in the streptococcus process, as they frequently are, the cavities should be kept clean by frequent syringing with a bland solution, such as the boric acid, or a warm normal salt solution. The latter has proved very serviceable in our hands. Frequently cleansing the nose of the muco-purulent discharge will go very far toward preventing middle-ear disease and even septic poisoning.

Drugs administered internally do not influence the course of the disease to any marked degree. We should, however, try to control special symptoms as they arise. If restless, the child should be quieted with morphine, paregoric or chloral hydrate, guarded with a stimulant. Such drugs as the tincture of the chloride of iron, chlorate of potash, quinine and strychnine are believed by many practitioners to be of service. Strychnine or digitalis is indicated when the pulse is weak and the arterial tension low. Above all, there is nothing of greater importance in the general management of these cases than stimulation and proper feeding.

When pseudo-diphtheria extends to the larynx, especially in early childhood, intubation will probably be required. Inhalation of steam generated under a croup tent will also prove of great service, especially when the primary disease is measles.

THE PATHOLOGY OF DIPHTHERIA.

Membrane.—The most characteristic clinical manifestation of diphtheria is the presence of a pseudo-membrane. This membrane may be located in various places along the respiratory and upper digestive tract. Lennox Browne,[1] in a clinical study of 1000 cases, found the membrane above the larynx in 841, or 84.1 per cent, of the cases. The fauces and tonsils were attacked in 672 cases and the fauces and nose in 165. The larynx, alone or with the fauces and nose, was affected in 159, or 15.9 per cent, of the cases.

Holt[2] found the membrane above the larynx in 63 cases, involving the larynx and structures below in 10 cases, and above and below the larynx in 36 cases.

In a careful study of 220 fatal cases of diphtheria, Councilman, Mallory, and Pearce found membrane at autopsy in 127 cases. It was distributed as follows:

	Cases.		Cases.
Tonsils	65	Tongue	9
Larynx	75	Stomach	5
Trachea	66	Duodenum	1
Pharynx	51	Vagina	2
Nares	43	Vulva	1
Bronchi	42	Skin of the ear	1
Soft palate and uvula	13	Conjunctiva	1
Esophagus	12		

[1] Diphtheria and its Associates, London, 1895. [2] Loc. cit., p. 957.

The membrane varies greatly in *appearance*; it may be whitish, grayish, chamois-colored, yellowish, brownish or almost black. Its density and consistence depend upon the amount of fibrin and other constituents. It is at times granular, friable and easily broken, and at other times, when the fibrin content is considerable, firm, dense and elastic. The membrane is more closely adherent to the faucial and laryngeal mucous membrane than to that of the lower respiratory tract, doubtless owing to the difference in the character of the epithelial cells. There is, as a rule, no difficulty in detaching it from the trachea without the production of an abrasion.

Councilman, Mallory, and Pearce distinguish, microscopically, two distinct varieties of the membrane corresponding to the differences observed macroscopically. The dense, firm, elastic membrane which can be stripped off in large flakes is composed of a reticular structure with beams of uniform size. The reticulum contains masses consisting of leukocytes and epithelial cells which have undergone hyaline degeneration.

The other variety of membrane, which macroscopically is characterized by greater friability, is composed of fibrin. The fibrin forms a reticulum just as does the hyaline material, but varies greatly in the size of the fibers and the spaces. The spaces may contain numerous leukocytes, either well preserved or broken down.

The fibrinous membrane is often continuous over the entire surface of the tonsil and extends into every crypt. The hyaline membrane never extends into the crypts, though occasionally small masses of hyaline reticulum are found in them.

The changes in the tissues observed by the above investigators are summarized as follows: The first step in the membrane formation is degeneration and necrosis of the epithelium, often preceded by active proliferation of the nuclei of the cells by direct division. The cells may either break up into detritus or become changed into refractive hyaline masses. An inflammatory exudation rich in fibrin factors comes from the tissues below, and fibrin is formed when this comes in contact with the necrotic epithelium. The fibrin in part is formed into a reticulum around exudation cells and degenerated epithelium; in part it combines with the hyaline degenerated cells to form a hyaline membrane. The latter is most often formed on those surfaces which are covered with epithelium having several layers of cells. The fibrinous membrane is formed both in the surface and in the tissues. The membrane is never formed primarily on an intact epithelial surface, but it may extend over it. There is nothing specific in the membrane formation in diphtheria, as typical hyaline and fibrinous membranes may be found in ovarian cysts in which bacteria play no part; but it is accompanied by degenerative and exudative changes in the tissue beneath.

The connective tissue and bloodvessels undergo a hyaline fibroid degeneration. Necrosis may extend deeply into the tissues, but there is little tendency to ulceration or abscess formation. The degeneration

in the mucous glands, particularly of the glandular epithelium, is so pronounced as to be almost specific. The extent of the necrosis in the primary lesions is greater than is found in the action of any other bacteria.

Diphtheria bacilli were never found growing in the living tissue or in connection with those degenerative changes in the epithelium seen in the beginning. They were found in the necrotic tissue and in the exudation, usually only in the latter. The bacillus shows an affinity for solid structures and is found rather on the reticulum than in the spaces between. The beginning of the lesions is probably due to the toxic action of the bacilli possibly growing in the fluids of the mouth or throat. When necrosis is once produced the necrotic tissue forms a suitable culture medium. The membrane and necrotic tissue are often invaded by phogenic cocci and by fungi.

Heart.—The pronounced clinical evidence of involvement of the cardiac muscle has led to extensive investigations of the underlying pathological changes in the heart. This subject has received careful study on the part of many pathologists.

One of the most important studies of the heart in diphtheria has been contributed by Romberg,[1] who made careful examinations in 8 cases. He found that the cardiac muscle was not uniformly affected, but that some portions might be normal and other areas show extensive changes.

Small foci of leukocytic infiltration were found around the smaller coronary arteries, but the most important lesion was the degeneration of the cardiac muscle. The degenerated fibers had a peculiar vacuolation in the center and were without nuclei. The nuclei undergo hypertrophy with an accompanying vesicular condition. The inner and outer portions of the myocardium showed most degeneration.

Focal interstitial changes, most common beneath the pericardium, were present in all cases. In 5 of Romberg's cases pericarditis was present and in 3 there was endocarditis.

Hesse[2] made a study of the heart in 29 cases of diphtheria. The parenchymatous changes were not marked under three days and were more pronounced on the left side. In 25 out of 29 cases interstitial myocarditis was present, and in 4 it was marked. It was noticeable in the first week, but was more pronounced later. The interstitial changes were more frequent in the left ventricle. The leukocytic infiltration was believed to be due to an increased penetrability of the vessel walls which were acted on by the toxin.

Councilman, Mallory, and Pearce have made an extended series of careful examinations of the cardiac muscle in 60 cases of diphtheria. The results of this valuable study are herewith presented: Fatty

[1] Ueber die Erkrankung des Herz muskels bei typhus abdom. Scharlach und Diphtherie, Deutsch. Arch. f. klin. Med., 1891, vol. **47**.

[2] Beiträge zur pathologische Anatomie des Diphtherie Herzens, Hahrb. f. Kinderh., 1893, vol. **36**.

degeneration of the muscular fibers, varying in extent, was found in 36 of the 60 cases; there were probably more than this number, as only 40 hearts were examined in the fresh state, and of this number 29 showed fatty change.

This degeneration varies in extent, at times affecting the myocardium generally, and at times in foci. The fatty change accompanies and appears to precede more advanced forms of degeneration which lead to complete destruction of the muscle.

The sarcous elements become swollen, broken and converted into hyaline masses. Vacuolation, fragmentation and fracture of the degenerated fibers are often seen. Simple fatty degeneration is found in severe cases of short duration, and the more extensive degenerations in protracted cases. The degenerations are due to the bacterial toxin, and account for the impairment of the heart function.

Two kinds of interstitial lesions are found. In the one there are focal collections of plasma and lymphoid cells, which may be accompanied by an independent myocardial degeneration, analogous to acute interstitial nephritis. In the other the interstitial change is secondary to the muscle degeneration. This form may lead to excessive connective-tissue formation and a fibrous myocarditis.

Thrombosis is not infrequently seen as a result of primary necrosis of the endocardium. The only bloodvessel change of interest is proliferation of the intima, which is also observed in other organs.

Lungs.—Pulmonary complications are present in a very large proportion of fatal cases of diphtheria and commonly determine the lethal outcome.

The lesion found is a bronchopneumonia of varying extent. Holt[1] says that in infants and young children bronchopneumonia is found at autopsy in at least three-quarters of the cases. Councilman, Mallory, and Pearce found bronchopneumonia in 131 out of 320 postmortem examinations; 98 of these were in cases of diphtheria only and 33 were in diphtheria complicated with scarlet fever or measles. The lung complication was much more frequently observed in patients in whom the larynx, trachea and the bronchi were the seat of membrane. It is believed that the most important factor in the production of these pneumonias is the aspiration into the lungs of microörganisms, chiefly micrococci.

Of the 131 cases of bronchopneumonia, the areas were discrete in 76 and confluent in 55. In the majority of cases the posterior portion of the lung was affected, and especially the lower lobes. The bronchi were affected in the majority of cases. The mucous membrane of the large tubes was reddened and covered with exudation; drops of pus could usually be forced from the small bronchi by pressing the cut surface of the lung.

In 43 cases there was a fibrinous exudation in the bronchi, forming

[1] Loc. cit.

in the larger ones a distinct membrane and completely filling the smaller.

Councilman, Mallory, and Pearce conclude that there is no organ in which lesions accompanying diphtheritic infection are so generally found or so serious as in the lung. In very many cases they are so extensive that death may be considered as due rather to the condition of the lungs than to the throat affection. The essential lesion is bronchopneumonia; true acute lobar pneumonia was never found. The cases resembling lobar pneumonia were found on close examination to be cases of extensive confluent bronchopneumonia. The character of the exudation varies; it may be fibrinous, hemorrhagic, serous, or almost entirely cellular; rarely it may be hyaline. Atelectasis is commonly present in varying extent, and the same is true of emphysema.

Considerable difference of opinion has existed as to the comparative influence of the diphtheria bacilli and other organisms in the causation of pneumonia complicating diphtheria.

Loeffler, in his study of the bacteriology of diphtheria in 1884, reported the presence of the diphtheria bacillus in the lung, but regarded it as a postmortem invasion.

In a series of 88 cases of diphtheria in which cultures were made from the lungs by Councilman, Mallory, and Pearce, the diphtheria bacillus was found in 49 cases, in 15 of which it appeared in pure culture. The streptococcus was present in 51 cases, in 15 of which it was found alone. The Staphylococcus aureus was noted in 27 cases and the pneumococcus in 10.

These writers conclude that, "Contrary to the results obtained from cultures, the pneumococcus must be considered the principal agent in producing the lung affection. The diphtheria bacilli are frequently found, and may be the cause of bronchitis with membrane formation, of purulent exudation, of bronchopneumonia, necrosis and abscess. They are often found in the lung in much greater numbers than in any other situation, and there may be but little change in the tissue around them."

It should be stated that Councilman, Mallory, and Pearce found the pneumococcus 59 times in microscopic sections and 11 times in cultures made from the same cases. Diphtheria bacilli were found 60 times in cultures and 38 times in sections; streptococci, 53 times in cultures and 29 times in sections.

Pleural Membranes.—Councilman, Mallory, and Pearce stated that in 18 cases there was pleurisy with fibrinous exudation, 1 with serofibrinous exudation, in 7 empyema, in 1 pyopneumothorax and in 1 hemorrhage into the pleural cavity. Small pleural ecchymoses, irregular in shape, were found frequently, chiefly over the surface of the lower and posterior lobes.

Spleen.—The changes in the spleen in diphtheria have been studied by Bizzozero, Oertel, Müller, Katzenstein, Ziegler, Ribbert, Waschkewitch, Babes, Flexner and Councilman, Mallory, and Pearce, by whom

the above writers are mentioned. Most of these observers describe, as the salient features of the alterations in the spleen, the presence of large, phagocytic, epithelioid cells in the lymph nodules and a necrosis of the lymphoid cells.

Councilman, Mallory, and Pearce state that there is but little change in the gross appearance of the spleen; it is generally firm, not distended, with smooth capsule. As a rule, the lymph nodules are distinctly visible on section, and at times very prominent. The size of the organ varies, but usually within normal limits. The spleen was examined microscopically in 181 cases, from the second to the one hundred and eighth day of the disease, and in subjects from ten months to sixty years of age. Most of the specimens examined were from patients under four years of age and under ten days' duration of the disease. The most conspicuous change in the lymph nodules was the formation of small areas composed of epithelioid cells of hyaline material and of a variable amount of nuclear detritus. This varied according to the duration of the disease.

The epithelioid formation usually occurred early and the hyaline change late. Such areas were found in 91 of 181 cases examined. The epithelioid cells were large, with variously shaped vesicular nuclei and finely granular protoplasm; they resembled the epithelioid cells found in tubercle. They were formed in the same way as those seen in the lymph nodes. The epithelioid cells are phagocytic and contain a nuclear detritus which is derived from the contained lymphoid cells.

In 17 of the 181 cases there was well-marked degeneration of the artery in the lymph nodules. The process was limited to the arteries in the lymph nodules. There was hyaline degeneration of the entire vessel wall in many cases, with the hyaline extending from the vessel into the tissue. The lumen of the vessel was narrowed and in some cases almost obliterated. This condition was most pronounced in the acute cases.

Changes in the veins similar to those described by Pearce in scarlet fever were found in 12 cases. These consisted chiefly of an accumulation of lymphoid and plasma cells beneath the epithelium of the intima.

Plasma cells were found in the spleen in large number in the later stages; this suggests that this organ may play an important role in their formation. No bacteria were found in the sections.

Alimentary Canal.—In 1888 Smirnow published a report of 6 cases of pharyngeal diphtheria in which distinct membrane was found in the stomach. The membrane resulted from an inflammatory, fibrinous exudation in 3 cases and in the other 3 it was due to a hyaline degeneration of the granular and surface epithelium.

Councilman, Mallory, and Pearce found 5 cases among 220 autopsies in which a definite diphtheritic membrane was present in the stomach. In one case almost the entire surface of the gastric mucosa was covered with a thick, ragged, grayish-brown membrane, which, on removal, left a red, granular surface beneath. In the other cases the formation of

the membrane was not extensive, and was limited to lines on the surface of the rugæ. Various bacteria were found in the membrane, but there were very few diphtheria bacilli. Upon culture, however, abundant bacilli were found in these cases.

The *intestinal mucous membrane* showed but few gross changes. It varied considerably in thickness, in some cases being decidedly atrophic. The most marked change was the hyperplasia of the lymphoid structures. Peyer's patches were in some cases so swollen as to resemble those seen in the early stage of typhoid fever. The swelling was rarely homogeneous, but the single lymph nodules or groups of them could be distinguished, forming round or elongated elevations with pits or furrows between them. The solitary lymph glands in both large and small intestines stood out prominently. Microscopic examinations were made in 60 cases. The changes in the intestinal lymph nodules were identical with but less pronounced than those in the lymph nodes generally. There was marked hyperplasia, and in 20 cases focal lesions, such as are seen in the spleen and lymph nodes. The vascular endothelium was swollen and proliferated, and often contained lymphoid cells.

Liver.—Oertel was one of the first observers to study the microscopic changes in the liver in diphtheria. He found small hemorrhages beneath the peritoneum and in the more superficial parts of the liver substance. He also noted a leukocytic infiltration of the subperitoneal and periportal connective tissue, with a fatty degeneration of the liver cells in the neighborhood of the cell invasion.

Councilman, Mallory, and Pearce examined the liver in 180 cases of diphtheria. There were no characteristic gross appearances. It was generally slightly swollen and somewhat tense and congested. In some cases the congestion was pronounced, but in others the liver was pale and cloudy, due largely to fatty degeneration.

Microscopically, the most constant lesion was swelling of the cells with increased granulation; this was most marked in the center of the lobules.

In place of the fine, even granulation of the normal cell, coarse granules of irregular size appear.

It was difficult to judge of the presence and degree of fatty degeneration. Many of the liver cells contained fat vacuoles. The most extensive fatty degeneration consisted of an actual necrosis of the liver cells. The necrosis was most marked about the hepatic veins and was always found affecting groups of cells. In most cases the necrosis is confined to the centers of scattered lobules; in others almost all the lobules in the section are affected. The disseminated foci were not so common as the central necrosis; they were found in but 7 of the 180 cases, whereas the central necroses were found in 22. The two processes were but rarely associated.

The lesions in the liver in diphtheria are not characteristic of the disease; similar changes are found in other infectious processes. No diphtheria bacilli were found in the microscopic sections. The hepatic

lesions in human diphtheria differ from those experimentally induced in animals, chiefly in the greater frequency of the central situation of the necroses.

Kidneys.—Councilman, Mallory, and Pearce examined the kidneys microscopically in 171 cases. The ages of the patients varied from two months to thirty years, and averaged three and three-quarter years. It was found possible to divide the kidneys into five classes according to the microscopic findings: (1) Those in which degeneration of the epithelium was the chief or the only lesion; (2) those in which acute interstitial changes consisting of cell accumulations in the vessels and interstitial tissue were present; (3) those in which the chief lesions were found in the glomeruli; (4) those in which hemorrhages into the tubules were present; (5) those in which chronic interstitial lesions were present, as shown by atrophied glomeruli and increase in the connective tissue.

1. **Degenerative Changes.**—Degenerative changes of varying grades were found in 112 of the 171 cases examined. Many kidneys, almost or quite normal in appearance, showed under the microscope a considerable degree of degeneration. The degeneration was slight in 26 cases, moderate in 38, marked in 37 and extreme in 9 cases. The most extreme degree was found in severe cases dying shortly after entry into the hospital.

Fatty degeneration, as determined by examination of frozen sections, was only slight in degree; it occurred in 44 out of 58 cases examined in this manner.

Some degree of hyaline degeneration was found in almost all the cases affecting prominently the proximal convoluted tubules. Casts were present in practically all of the cases, especially when the hyaline degeneration was pronounced.

The most constant change seen in the glomeruli consisted of a small amount of granular coagulum between the tuft and the wall.

In 40 cases of simple degeneration the urinary record is available. Albumin was found in 33 of the cases. There was, with some exceptions, a general agreement between the presence of albumin and the degree of degeneration.

There appeared to be no relation between the character of the degeneration and general infection with various bacteria. In the 110 cases a general infection with diphtheria bacilli was noted in 20 cases, with the streptococcus in 29 cases, with the Staphylococcus aureus in 4 cases and with the pneumococcus in 3 cases. In the 9 cases of severe degeneration general infection was noted but once, and that with the streptococcus.

2. **Acute Interstitial Changes.**—Acute interstitial nephritis, evidenced by infiltration of the interstitial tissue with cells of the plasma type, was present in 43 of the cases. The kidneys were but slightly, if at all, enlarged, save in the most marked cases, when considerable swelling was present. The interstitial infiltration was general in all parts of

the kidney, but was more intense in foci; most of the cells were plasma cells with typical nucleus and protoplasm. Lymphoid cells and, in severe cases, large phagocytic cells were also present. The amount of epithelial degeneration varied in different cases.

The infiltrating cells were usually limited to the interstitial tissue; the changes were accompanied by alterations in the vessels, the cell infiltration at times almost obscuring them. The degeneration found in foci of intense infiltration appears to depend on malnutrition resulting from blocking of the vessels by the cells.

In all of the interstitial cases the duration of the disease was more prolonged than in the case of simple degeneration. The average duration of the illness was twenty-one and a half days. The interstitial process apparently takes some time for its development, and the cases dying early do not, as a rule, show the process at its maximum. Mixed infections with scarlet fever and measles are more apt to cause interstitial changes than simple degeneration. The urine was tested for albumin in 15 cases, in 14 of which it was found present.

3. **Glomerular Changes.**—This variety of the disease was found in 11 cases, in all of which the glomerular changes were the predominating ones. Lesions of the glomeruli were uncommon in the cases of simple degeneration and in those showing interstitial involvement.

The first evidence of change in the glomeruli is increase in the number of cells. The endothelial lining of the vessels undergoes proliferation and occludes the vessel. Later a hyaline degeneration of the cells and the vessel walls takes place.

Glomerular nephritis was present in subjects averaging a greater age than the degeneration and interstitial cases. The average duration of the disease at the time of autopsy was also greater.

4. **Hemorrhage.**—Slight hemorrhages in the kidney were seen in 3 cases, but true hemorrhagic nephritis was noted in but 1. The red blood cells were found chiefly in the tubules and the interstitial tissue. The rarity of hemorrhagic cases was considered surprising.

5. **Chronic Cases.**—In 4 cases chronic changes were present, as evidenced by atrophy of the tubules and increase in connective tissue. In these cases death occurred at entirely too early a date to attribute the changes to diphtheria; the lesions were evidently due to some antecedent disease.

Councilman, Mallory, and Pearce conclude that lesions of the kidney, varying from simple degeneration to the more serious conditions of acute nephritis, are found in all fatal cases of diphtheria; there is, however, no type of lesion peculiar to the disease.

Lymph Nodes.—Councilman, Mallory, and Pearce examined the lymph nodes in 109 cases. They were constantly the seat of pathological changes.

The nodes most involved are those nearest to the seat of exudate—the tonsils and the cervical glands. The distant nodes are very rarely affected.

The lesions are most pronounced in severe cases, in which a fatal termination occurs early. Two varieties of lesions are described.

1. The ordinary lesions, which may follow an injury of almost any sort and which consist in congestion, hemorrhage and diffuse and circumscribed necrosis. Numerous new cells are found which are derived partly from the lymphoid cells and partly from proliferation of the endothelial cells of the sinuses and reticulum. The swelling of the nodes is due chiefly to congestion, hemorrhage and dilatation of the sinuses; the lymphoid cells do not increase perceptibly in number.

2. Lesions which are distinctive of diphtheria, but which may be found in other infectious diseases in children. Foci are formed which are similar in appearance to miliary tubercles; these are the result of a combination of processes—proliferation, phagocytosis and degeneration. Large epithelioid cells are formed from proliferation of the endothelial cells of the reticulum and vessels. These devour lymphoid cells, and they themselves ultimately undergo necrosis. Bacteria seem to exert no direct influence in the production of these lesions, and were not found in the nodes.

The lesions are believed to be due to the absorption of the toxic products of the diphtheria bacilli and other organisms.

The lesions found in the tonsils differed somewhat from those seen in other lymphoid structures. They were constantly present, and in most cases more pronounced than in the glands.

Thymus.—Flexner studied the changes in the thymus gland in experimentally induced diphtheria in animals. He called attention to the frequency with which the degenerated cells occurred in the neighborhood of the Hassel bodies. The changes in general were similar to those observed in the lymph nodes.

Councilman, Mallory, and Pearce examined the thymus in 20 cases. The principal change found was degeneration of the lymphoid cells. The degenerated cells were usually seen in large cells with vesicular nuclei; the changes were most marked in the vicinity of the Hassel bodies. There was dilatation of the lymphatics and hyaline degeneration of the walls of the vessels. No bacteria were found in the sections.

Skeletal Muscles.—Councilman, Mallory, and Pearce state that where fatty degenerations of the heart and the nervous system are present, a similar change will be found in the skeletal muscles. In one case in which the nerve fibers of the central nervous system and of the peripheral nerves showed marked fatty degeneration, the muscles of the tongue, of the ulnar side of the forearm, the sartorius muscle and the biceps of the thigh exhibited a similar degeneration.

In another case where fatty degeneration of the heart and nervous system was pronounced, the muscles of the tongue, the diaphragm and the tibialis anticus were likewise degenerated.

Pancreas, Adrenals, Thyroid Gland, Salivary Glands, Testicles, Pituitary Body.—No gross changes were observed in these glands by Councilman, Mallory, and Pearce; neither did a careful microscopic examination reveal the presence of pathological changes.

In one case the submaxillary gland showed superficial necrosis and purulent infiltration due to extensive inflammation from the throat.

Welch, Flexner, and Wright commonly observed congestion, hemorrhage and focal necrosis in the adrenal glands in experimental diphtheria, but such changes apparently do not occur in this disease in the human subject.

Nervous System.—Councilman, Mallory, and Pearce refer to a study of certain nerve structures made in 28 of their cases by Thomas and Steensland. The cases were selected either on account of the presence of cardiac symptoms, paralysis or the severity of the disease. Various cranial and other nerves were submitted to careful microscopic study. In all of them some grade of fatty degeneration was noted. The degeneration seems almost invariably to begin in the myelin sheath. The change in the axis cylinder consits chiefly of an irregular swelling which often causes it to present a beaded appearance.

The cerebrum was examined in 5 cases, the cerebellum in 2, the pons in 3, the medulla in 4 and the cord in 7 cases. In all of these examinations a varying degree of fatty degeneration was present in the white substance. The same change was noted in the anterior and posterior nerve roots.

In general it may be said that a slight to a marked diffuse fatty degeneration, involving the central nerve fibers and their peripheral extensions, occurs in certain cases of diphtheria.

Bone-marrow.—Councilman, Mallory, and Pearce examined the bone-marrow in 48 cases of diphtheria. Of this number all but 3 were children. In all of the cases the marrow was hyperplastic, although in the 3 adults the hyperplasia was less pronounced. In the latter the marrow was reddish with areas of yellow fat.

In the children the marrow varied in apearance, but was usually red, of firm consistency, and removable in solid pieces.

Very little connective tissue was found in the marrow, and that was along the arteries. The veins were numerous and the walls like those of capillaries; it is through these thin walls that the marrow cells appear to enter the blood.

The changes in the marrow in diphtheria are not distinctive of the disease, as they are also found in other infectious diseases.

Blood.—During the first few days of the disease the *erythrocytes* are about normal in number, according to the investigations of Morse, Ewing, Engel, and Billings. From the fifth to the fifteenth days, Billings observed an average loss of 510,000 cells per cubic millimeter. The loss ranged from 470,000 on the third day to 2,040,000 on the sixth. These were cases not treated by antitoxin. Of 23 severe and carefully counted cases treated with antitoxin, 3 alone exhibited a reduction in the erythrocytes, the loss being less than 400,000 cells per cubic centimeter.

Cabot remarks that "Antitoxin largely prevents the anemia which usually develops in the first five to ten days." Healthly persons

receiving antitoxin, according to a study of 15 cases by Billings, show a moderate loss of red cells in about one-half of the cases; the greatest diminution observed was 930,000 per cubic millimeter.

A reduction in the *hemoglobin* occurs coincidently with the diminution in the number of red cells, but restoration of the former takes place more slowly than the latter. Billings states that in cases treated without antitoxin an average loss of 10 per cent was noted; whereas, when antitoxin was administered the reduction of the hemoglobin was less marked.

Gabritschewsky, in 1894, was the first to point out the more or less constant hyperleukocytosis in diphtheria. He demonstrated by animal experimentation that the increase in the *leukocytes* was due to the action of the diphtheria toxin.

Morse found a leukocytosis in 26 out of 30 cases, Ewing in 49 out of 53 and Billings in 34 out of 36 cases. The grade of the leukocytosis is in a general way proportionate to the severity of the disease. Morse observed very high counts in the fatal septic cases.

Cabot says that when leukocytosis is absent the cases are either very mild or very severe, conditions analogous to those noted in pneumonia and septicemia. The counts ranged from normal to 48,000 (Morse), or to 38,000 (Billings). Bouchut counted over 75,000 white cells per cubic millimeter in some of his cases, and Felsenthal found 148,229 in one case.

The white cells ordinarily increase as the disease progresses, and decrease as convalescence sets in.

According to Ewing, the leukocyte count is not influenced by the use of the antitoxin serum, except during the first twenty-four hours after its injection. Within thirty minutes the leukocytes are said to be considerably diminished.

Engel states that antitoxin in the beginning causes a slight increase in the percentage of lymphocytes; in some cases the increase is pronounced. In one case after injection they rose from 24 to 65 per cent.

Engel also emphasizes the bad prognostic import of the presence of a considerable number of myelocytes.

It is generally conceded that an examination of the blood in diphtheria lends little or no aid in diagnosis. The absence of leukocytosis and the presence of a considerable number of myelocytes would seem to be of ill augury.

THE DIAGNOSIS OF DIPHTHERIA.

As diphtheria is a communicable disease with a decided predilection for young children, among whom it is also most fatal, it is important that an early diagnosis should be made, both with regard to prevention and treatment. Without a history of previous exposure to the infection it is confessedly difficult to recognize the disease in its very earliest

manifestations; for there is no throat affection more varied in its clinical aspect and more deceptive in its initial stage than diphtheria. But, fortunately, the disease is not long in revealing its true nature. In the majority of cases the diagnosis is not difficult after the affection has continued for twenty-four hours, since by this time the characteristic exudation may be seen on the tonsils or some part of the fauces. When thus clearly marked the nature of the throat disease is at once apparent on the first examination.

But all cases are not so readily diagnosticated, even by experienced physicians. Neglecting to inspect the throat of a child, who is feverish and indisposed, may sometimes be a reason for failure in making an early diagnosis. While sore throat is one of the earliest symptoms of diphtheria, yet it is a fact that many children, even those old enough to make known their sensations, do not complain of the throat until the disease has made considerable progress.

On his first visit to a child, on account of whose illness he has been summoned, the physician should be careful to examine the fauces, especially when diphtheria is prevailing in the neighborhood. In this way the disease may be discovered early and its spread to other members of the family prevented.

In well-marked cases it is usually not difficult to make the diagnosis. In doubtful cases it may be helpful to know whether the patient has been recently exposed to the infection of diphtheria, scarlet fever or some other infectious disease. If exposure to diphtheria is known to have occurred, the mildest form of sore throat should be regarded with suspicion and carefully watched for further development. But, in a section of the country where diphtheria is not prevailing it is probable that a sore throat presenting some of the characteristics of the disease will turn out to be something else.

It sometimes happens that an early diagnosis is not made because the exudation is concealed in the crypts of the tonsils, or in some other depressions of the faucial surface. When thus located it may be brought into view by pushing the tongue depressor far back on the tongue and causing the child to retch slightly; or these surfaces may be exposed to view by having an assistant make firm pressure on the neck near the angle of the jaw while an examination of the throat is being made.

In some cases it is impossible to make a positive diagnosis clinically until the disease has been under observation for two or three days. This is more especially true in some forms of nasal diphtheria, without involvement of the fauces to a greater extent than the occurrence of a general hyperemia. The uneven surface of the cavities of the nose favors concealment of the disease until it has made some progress. It may then be discovered either by inspecting the nares at their external orifices, or by an examination with a nasal speculum. In nasal diphtheria there is apt to be a muco-purulent discharge from the nose, and when there are seen in this discharge small, white specks,

exudate is probably present, although it may not yet be visible. It usually, however, makes its appearance before the disease terminates.

There are no prodromata that are peculiar to diphtheria. The general malaise, followed by headache, nausea and vomiting, so commonly seen, are the forerunners of many other affections also. Even the sore throat, pain in swallowing, tenderness of the glands near the angle of the jaw and swelling of the neck are all present in the ordinary forms of tonsillitis. The distinguishing feature of diphtheria is the peculiar exudation that appears upon the mucous membrane, particularly in the fauces. A knowledge of the fact that this exudation takes place not only into the epithelium, but also into the subepithelial tissue, is helpful only to a limited extent in solving the problem of diagnosis. Indeed, in many severe cases the diphtheritic process does not penetrate deeply into the mucous membrane, as it peels off quickly and leaves only small areas of superficial ulceration. On the other hand, an exudation of streptococcic origin is sometimes very adherent, and its disappearance may be followed by marked ulceration of the mucous membrane. But in most streptococcic affections of the throat, certainly in the milder varieties, the disease is limited to the tonsils, and the greater part of the exudation may be removed with a cotton swab.

In considering the diagnostic feature of the diphtherial membrane it is necessary to recall some of its characteristics already described. It is deposited not only on the tonsils, but frequently also on the pillars of the fauces, the soft palate, the pharyngeal wall, in the nares and in the larynx. One of the peculiarities of the membrane is that it is liable to start on some of the small prominences of the fauces, such as the uvula, epiglottis and the like. As already mentioned, it is also liable to form in some of the small recesses, such as the lacunæ of the tonsils and the ventricles of the larynx. The formation of membrane on the uvula, especially on its posterior surface, is believed by some writers to be almost pathognomonic. When seen on the sides of the uvula it is quite sure to be present on its posterior surface also. Frequently the entire uvula is invested with membrane, which is often shed as a complete cast, resembling, as Trousseau has said, the finger of a glove.

When the diphtherial exudation is examined carefully it is found to be distinctly membranous. It is of a yellowish-white color, and when exfoliated in large pieces or casts and allowed to float in water it bears a strong resemblance to pieces of chamois skin. Lennox Browne's description of the exudation is worth repeating. He says it "Begins almost invariably as a thin, bluish-white deposit, something like a shaving from the boiled white of an egg of the duck, goose or plover. As the deposit increases in thickness, it gradually becomes more white and opaque, resembling the boiled albumen of a fowl's egg, or it may then partake of a very pale lemon tint. Then it becomes of a yellowish- or greenish-gray, brown, and sometimes almost black, as the necrotic process advances, or as blood is extravasated. Only in the

comparatively uncommon case of a lacunar diphtheria do we see the exudation commencing as discrete spots in deposit, which may be of a yellow color at the very first onset, and, even when coalesced, may never exhibit the pearly or opalescent appearance which characterizes the more ordinary form on its first manifestation." He adds, "The membrane is sometimes plastered, as if put on with a palette knife, or laid on with a trowel." This latter comparison applies with much aptness to what is seen when the entire fauces and soft palate are covered with the exudation.

Adenitis, or more or less enlargement and tenderness of the lymphatic glands of the neck, is a symptom rarely absent. Its importance depends to some extent on the region in which the glands are involved, and the degree of inflammation and swelling. In mild tonsillar diphtheria the cervical glands alone are swollen, but, as a rule, only very slightly. In the more severe cases, including the complex or septic form of the disease the whole chain of cervical glands is converted into one large mass. The inflammatory enlargement includes also the periglandular cellular tissue. In such cases not only the cervical, but the submaxillary and sometimes the parotid glands are affected.

Catarrhal Croup.—There is frequently some difficulty in distinguishing between membranous croup in its early stage and catarrhal, spasmodic or non-specific croup. But if a few of the principal points of difference be borne in mind the difficulty should not be very great. For instance, in membranous croup the symptoms are progressive, being as well marked in the day-time as in the night. The hoarseness gradually increases, so that the child in a short time can speak only in a whisper. The breathing becomes more and more obstructed as the exudation increases; the temperature reaches 100° to 103° F., and the child constantly grows more restless and cyanotic. There is marked recession of the ensiform process of the sternum and of the lower ribs. These symptoms are not relieved by the relaxing influence of an emetic. Moreover, the characteristic exudation may be present in the fauces. On the other hand, in catarrhal or spasmodic croup the symptoms are usually intermittent, being due to a paroxysmal spasm of the glottis, resulting from subacute laryngitis. In the vast majority of instances the affection occurs at night-time, and more often in the early part of the night. During the day the symptoms, if present at all, are usually much more moderate. The duration of the paroxysm varies from a few minutes to several hours. The voice, though hoarse, is very rarely quite extinct or whispering, and scarcely ever more than than temporarily so. This is a diagnosic point of much value in distinguishing between the two forms of croup. In spasmodic croup an emetic generally gives relief, but does not in membranous croup. The fauces are free from exudate.

Vincent's Angina.—We have already remarked that a membranous sore throat, in which the spirochete and fusiform bacillus of Vincent in association with the streptococcus are the principal if not the sole

organisms present, sometimes occurs, and we have pointed out some of the characteristics of this affection in comparison with those of true diphtheria. We repeat that, as a rule, in true diphtheria the exudate is so intimately connected with the mucous membrane that it cannot be removed without injuring the parts, while in Vincent's angina it lies upon the surface and may be quite readily removed. It must be admitted, however, that there are many exceptions to this rule. The physician, therefore, will often find it impossible to make a positive diagnosis without a culture and a microscopic examination. (See Chapter XVIII.)

Follicular Tonsillitis.—There is perhaps no throat affection more often mistaken for diphtheria than follicular tonsillitis. It is a very common disease, being more frequently seen in some families than in others. It sometimes spreads as though it were contagious. It begins with sore throat, fever and tenderness in the neck below the angle of the jaw. There is often a good deal of constitutional disturbance, such as high temperature, headache, and chilliness, and sometimes pain in the back and extremities. The fauces at first are hyperemic, but the tonsils soon become enlarged and dotted over with rounded masses of whitish material of pin-head size. These dots frequently coalesce, forming quite large patches, particularly in the crypts of the tonsils. The dots or patches consist of a peculiar secretion having incorporated with it epithelial cells. It differs from the diphtherial exudate in that it is readily detached by a swab. The cheesy dots that form on the tonsils will, when crushed between the thumb and finger, emit a fetid odor. The disease is of short duration, and is not followed by sequelæ. The diagnosis is easily made, except in some cases of the mildest form of diphtheria when differentiation may be difficult. In acute quinsy the jaws are stiff, and there is often considerable difficulty in opening the mouth sufficiently wide for a satisfactory inspection of the fauces. Where any doubt is felt as to the nature of the affection it may be readily dispelled by a bacteriological examination.

Herpetic Pharyngitis.—There is usually no great difficulty in recognizing an herpetic pharyngitis, but, like follicular tonsillitis, it is occasionally mistaken for mild diphtheria. If seen in the early stage, before the minute vesicles have disappeared, the diagnosis is easily made; but the ulcers that remain often show a whitish covering, which has often been mistaken for diphtherial exudate. As the ulcers are very small, the whitish concretions are usually seen in the form of dots. It is only when these concretions unite and form a patch that any difficulty is experienced in the diagnosis. It has been said that the presence of an herpetic eruption on some other part of the body would afford presumptive evidence that the throat affection was of the same nature, but we have often seen herpes labialis in children suffering from diphtheria. Fortunately, in these diseases the clinician does not have to base his diagnosis upon symptoms alone; he can invoke the aid of bacteriology.

Gangrenous Pharyngitis.—In our experience gangrenous pharyngitis is rare in diphtheria. We do not recall having seen a single case. The affection, however, is not uncommon in scarlet fever. The ulcerative action and loss of tissue are much more extensive than that which is seen in diphtheria. The necrotic tissue resulting from the gangrenous process has often been mistaken for diphtherial exudate. The pseudo-membrane in this variety of sore throat is, from the beginning, of a dark gray or brownish color, and is exceedingly offensive. On the other hand, the pseudo-membrane of diphtheria is white or yellowish-white in the commencement, and continues so to the end unless it becomes stained with blood. The fetor in the latter disease is mild in comparison with the former. The diagnosis is not difficult if the case comes under observation at the beginning.

Stomatitis.—In diffuse inflammation of the mucous membrane of the mouth the small ulcers that commonly appear show a whitish covering. This condition not infrequently increases to the extent that many of these ulcers coalesce, forming patches consisting of a whitish, curd-like matter; and the affection often extends gradually to the roof of the mouth, the inside of the cheeks and may even reach the pharynx. The exudation is usually thin, and sometimes covers evenly a large part of the mucous membrane of the mouth, but more commonly it is seen in irregularly scattered patches and points. When the disease assumes this appearance it is occasionally confounded with diphtheria. In making a diagnosis it is important to note that the exudation is thin and filmy; it never becomes membranous. On parts where it is thicker it is curdy or cheesy.

We have known *gangrenous stomatitis* and even *syphilitic sore throat* to have been mistaken for diphtheria. In view of the general characteristics of these affections the diagnosis is not difficult.

The presence of *albumin* in the urine in diphtheria deserves some notice as a diagnostic sign. We have found it in quite a large proportion of our cases in which the urine was examined. Its presence would be of still greater diagnostic importance were it not true that it is occasionally found in some other varieties of inflammation of the throat.

Since the advent of bacteriology as a science the clinician has at his command a most useful means of determining the diagnosis of diphtheria in all doubtful cases. While every well-informed physician should be familiar with the clinical evidences of the disease, yet as the clinical disguises of this throat affection are so varied it is fortunate that the doubtful points of diagnosis can be solved by bacteriology. Therefore, any consideration of the subject of diagnosis in diphtheria would be regarded as incomplete at the present day without some reference to the means employed to determine the presence of the Klebs-Loeffler bacilli in the pseudo-membrane.

The Bacteriological Diagnosis of Diphtheria.—In a patient presenting suspicious clinical evidences of diphtheria, the diagnosis may be

firmly established by determining the presence or absence of the diphtheria bacilli in the false membrane. This may be accomplished by examination of (*a*) smears and (*b*) cultures.

Smears.—In a large percentage of cases a satisfactory result may be obtained from an immediate microscopic examination of the exudate present. A cover-glass is smeared with material taken from the throat by means of a swab. The cover-glass preparation is allowed to dry, is then passed several times through a flame to fix the albumin, and is finally stained with Loeffler's solution of methylene blue. By this means the presence or absence of bacilli may often be determined in a few minutes.

The rapidity with which the examination can be made makes it a procedure of great value, particularly where an immediate diagnosis is a matter of great importance. We have examined a considerable number of smears at the Philadelphia Hospital for Contagious Diseases, and in these cases we were enabled in the vast majority to predict the subsequent cultural findings.

The procedure just mentioned, however, has only a relative value and should not be depended upon to the exclusion of the culture. The bacilli found in smears are ordinarily much less typical than those grown upon culture media, and the chances of contamination are greater.

Cultures.—Cultures are ordinarily made with a swab, although a platinum loop may be employed for the purpose. The swab consists of absorbent cotton wrapped around the end of a piece of heavy wire. The swab, enclosed ordinarily in a plugged test-tube, is sterilized by heat.

In taking the culture the tongue should be depressed by means of a spoon or depressor, and the swab firmly rubbed over the surface of the membrane. When no membrane is present the swab should be brought in contact with the tonsils, faucial pillars and pharyngeal wall. When laryngeal symptoms alone are present, the swab should be introduced as far down as possible. The moistened cotton is then rubbed lightly over the surface of a tube of Loeffler's blood serum, care being taken to carefully replace the cotton plug. The swab containing the remains of the infected material should be returned to its own tube and subsequently destroyed or disinfected.

Great care should be taken not to make the culture directly after antiseptic applications have been applied to the throat. It is well, in such cases, to wait one-half hour or one hour before culturing. The inoculated tubes are incubated at a temperature of from 99° to 100° F. (37° C.) for twelve to fourteen hours, at the end of which time the colonies may be examined.

The gross appearances of the culture are more characteristic at the end of twenty-four hours. The diphtheria bacillus grows so much more rapidly than other mouth organisms upon the surface of Loeffler's blood serum that they are often the only conspicuous colonies present.

The colonies are large, round, grayish-white or cream-colored, elevated with irregular periphery, which is less dense in the center.

Examination of Cultures.—A drop of sterile water is placed upon a clean cover-glass and rubbed up with a couple of colonies which have been detached from the culture media with a platinum loop. The preparation is allowed to dry in the air and is then passed several times through the flame of a Bunsen burner or alcohol lamp. It is then covered with Loeffler's alkaline solution of methylene blue for ten minutes, after which it is rinsed, dried and mounted in balsam.

The specimen is examined with $\frac{1}{12}$-inch oil-immersion lens. Diphtheria bacilli may be found in pure culture, or micrococci of different varieties may also be present.

Practical Value.—The bacteriological examination of suspicious cases of diphtheria is capable of both great benefit and great harm.

If the culture is *thoroughly* rather than carelessly made, and especially from between the membrane and the tissues, positive results are observed in fully 98 per cent of cases. Under these conditions the chances of error on the *first* culture are but 1 to 2 per cent and a second culture is almost sure to detect these. But if the culture is made in a haphazard manner, and especially by the superficial swabbing of heavy exudates, diphtheria bacilli may be missed in from 15 to 20 per cent of cases. This constitutes the menace of the bacteriological method, since physicians may permit themselves to be misled by a primary negative culture. In other words, *a great deal of the value of the bacteriological diagnosis of diphtheria rests upon the shoulders of the physician making the culture;* if he fails to swab up the bacilli which are *deep* in the exudate they cannot be found in the smear or culture tube no matter how skilfully and thoroughly they may be examined.

Bacteriological examinations, therefore, should never be relied upon entirely in the diagnosis of diphtheria and *in suspicious cases at least two negative cultures should be required before diphtheria is excluded.* In our opinion the common practice of relying upon a single negative culture is one fruitful source of diphtheria in our midst as a result of missed diagnoses. When diphtheria is suspected it is always well to give antitoxin at once, even though this means its needless administration in some cases, in order to spare infected individuals the dangers of delayed or missed diagnosis.

In the absence of membranes and typical lesions bacteriological examinations are indispensable in diagnosis; also in the diagnosis of nasal diphtheria when patches of exudate are hidden from view. Unfortunately non-virulent diphtheroid bacilli are widely distributed and may be found in the nose or throat in the absence of diphtheria, but these are usually of the short solid types readily differentiated from the more dangerous granular and barred bacilli. Furthermore the guinea-pig-virulence test is thoroughly reliable for differentiation when properly conducted.

Virulent bacilli may be present weeks and months after recovery

when the patient has developed an antitoxin immunity, but these organisms are capable of infecting non-immune individuals. A negative Schick reaction, therefore, does not exclude the possibility of the presence of virulent bacilli. On the other hand, the bacilli recovered in cultures over weeks and months after recovery may be non-virulent and harmless and it is unnecessary to quarantine the carrier, but this can be determined only by carefully conducted guinea-pig tests. Every board of health laboratory should be prepared to conduct these tests when quarantine is prolonged by reason of positive cultures in order to protect both physicians and patients against unnecessary hardship and to better gain the coöperation of the former in the proper management of diphtheria from the public health standpoint.

THE PROGNOSIS OF DIPHTHERIA.

The forecast of diphtheria cannot be made with any degree of certainty. The disease itself, to say nothing of the complications that are liable to occur, is so treacherous that it is almost impossible to predict a favorable ending of any attack however mild the earlier symptoms may be. Not infrequently cases that appear to be mild in the beginning and give the best promise of recovery suddenly change into a severe form through extension of the diphtheritic process into the larynx, or the development of some dangerous secondary affection. On the other hand, cases that begin with marked severity, giving rise to gloomy forebodings, often take a favorable change and speedily end in recovery.

So variable are the elements of prognosis in diphtheria that they cannot be considered from any single standpoint. One must take into consideration the prostrating effects of the toxins of the disease; the history, environment and age of the patient; the complications affecting vital parts during the course of the attack and the nature of the sequelæ. Likewise, the character of the prevailing epidemic must be taken into account. In some epidemics a large proportion of the cases are mild and the death-rate is low. In other epidemics, or in some localities the disease assumes a more severe form, and, in spite of the best treatment, the proportion that perish is much larger. A death-rate as high as 60 per cent has been reported, while in very mild epidemics it has been as low as 5 to 10 per cent.

It is a question whether *social status* and *domestic surroundings* have as much to do in determining the character of the disease as is generally supposed. It is true, however, that when diphtheria breaks out in an institution for children, especially foundlings, it is apt to be attended with great fatality. In our experience the patients sent to the hospital from careless and indigent families are not more liable to suffer from severe diphtheria than those which come from better and more sanitary homes. Nor do we find that delicate children perish in a larger proportion than the robust. In speaking of the influence

exerted by social status, Lennox Browne says it has appeared to him "That when diphtheria attacks members of the upper classes it is often more malignant, and runs a more quickly fatal course than among the indigent; the disease finding, as it were, a more receptive soil in the case of those delicately nurtured than in those whose systems are in a manner accustomed to insanitary influences. On the other hand, and for obvious reasons, recovery from the sequelæ, when once the acuteness of the attack has passed off, is more expeditious and complete in the well-to-do."

There can be no doubt, however, that when diphtheria is at all severe unsanitary surroundings would contribute toward an unfavorable prognosis. The less adequate the facilities for caring for the patient and the poorer the service, the greater are the probabilities that the disease will spread and increase in virulence. Where no attention is paid to ventilation of the sick-room, the vitiated condition of the atmosphere tends to lower the resisting power of the patient, and thus diminishes the chances of recovery.

Age.		Admitted.	Died.	Percentage.
Under 1 year	1892	49	31	
	1893	40	37	
		89	68	76.4
1 to 2 years	1892	108	66	
	1893	166	106	
		274	172	62.7
2 to 3 years	1892	163	90	
	1893	219	131	
		382	221	57.8
3 to 4 years	1892	195	96	
	1893	296	149	
		491	245	49.9
4 to 5 years	1892	240	106	
	1893	339	143	
		579	249	43.0
5 to 10 years	1892	631	163	
	1893	880	233	
		1511	396	26.2
10 to 15 years	1892	209	15	
	1893	298	30	
		507	45	8.8
Over 15 years	1892	414	16	
	1893	610	36	
		1024	52	5.0

Idiosyncrasy, or any family susceptibility to diphtheria that may be known to exist, should be taken into consideration as affording important prognostic data. Every practitioner knows how fatal the disease is in some families. It is worthy of notice that when diphtheria breaks out in a family, or in a neighborhood, children are almost always the first to be attacked, showing that in them the susceptibility to the disease is most marked.

Age.—There is not only an age disposition to diphtheria, but there is also an *age mortality*, and this must be taken into account in a forecast of the disease. The vast majority of all deaths from this affection occurs among children under five years of age, and the mortality-rate at this age period is vastly higher than in any other quinquennial period of life. This statement is confirmed by the statistics of all large hospitals for the treatment of diphtheria patients.

The table on p. 683 shows the mortality, according to age, in the Asylums' Board Hospital, London, 1892–1893:[1]

Of 1000 consecutive cases of diphtheria observed by Lennox Browne the age mortality was as follows:

Age.	No. of cases.	Deaths.	Percentages.
Under 1 year	11	5	45.45
1 to 2 years	71	45	63.38
3 to 3 "	85	34	40.00
3 to 4 "	117	54	46.15
4 to 5 "	118	43	36.44
5 to 6 "	108	34	31.48
6 to 7 "	84	24	28.57
7 to 8 "	57	9	15.78
8 to 9 "	31	11	35.48
9 to 10 "	38	5	13.15
10 to 11 "	29	8	27.58
11 to 12 "	20	0	
12 to 13 "	16	0	
13 to 14 "	22	2	9.00
14 to 15 "	15	2	13.33
Over 15 "	178	7	3.93
	1000	283	28.30

Classified according to quinquennial age periods, the cases in the above table show as follows:

Age.	No. of cases.	Deaths.	Percentages.
Under 5 years	402	181	45.00
5 to 10 "	318	83	26.10
10 to 15 "	102	12	11.70
Over 15 "	178	7	3.93
	1000	283	28.30

In the following table of statistics, including over 9000 cases of diphtheria which were treated in the Philadelphia Hospital for Contagious Diseases, during a period of ten years, from 1893 to 1902, inclusive, the number of patients and the mortality-rate within certain age periods are shown:

[1] Browne, Lennox: Diphtheria and Its Associates.

Year.	Under 1 year.			1 to 5 years.			5 to 10 years.			10 to 15 years			15 to 25 years.			25 years and upward.		
	Admitted.	Died.	Per cent.	Admitted.	Died.	Per cent.	Admitted.	Died.	Per cent.	Admitted.	Died.	Per cent.	Admitted.	Died.	Per cent.	Admitted.	Died.	Per cent.
1893	3	2	66.66	82	35	42.68	53	17	32.07	18	3	16.66	36	3	8.33	25	2	8.00
1894	16	9	56.25	218	98	44.95	120	36	30.00	31	6	19.35	52	3	5.77	28	2	7.14
1895	25	10	40.00	327	122	37.30	187	43	22.90	46	7	15.20	56	4	7.10	65	4	6.10
1896	33	18	54.54	404	128	31.68	276	35	12.68	71	5	7.04	49	1	2.04	36	3	8.33
1897	34	16	47.05	560	199	35.53	437	65	14.87	126	14	11.11	89	3	3.37	49	3	6.12
1898	42	20	47.61	552	200	36.23	447	66	14.76	93	8	8.60	47	3	6.38	48	0	
1899	38	24	63.15	659	181	27.46	462	59	12.79	102	7	6.81	62	2	3.22	50	2	4.00
1900	40	21	52.50	595	192	32.27	473	71	15.01	117	7	5.98	90	4	4.44	52	3	5.76
1901	30	15	50.00	374	119	31.81	287	28	9.75	106	5	4.71	56	6	10.71	36	1	2.77
1902	38	12	31.57	305	97	31.08	159	25	15.72	40	1	2.50	33	2	6.06	26	0	
	299	147	49.16	4076	1371	33.63	2901	445	15.33	750	63	8.40	570	31	5.43	415	20	4.81

Sex.—We see no reason why sex should exert any influence on the mortality-rate, and yet according to our observation, as well as that of some other writers, the death-rate among the males is almost constantly in excess of that of the females.

The following table shows the mortality, *according to sex*, of all cases of diphtheria treated in the Asylums' Board Hospitals, London, from 1888 to 1894, inclusive:[1]

Sex.	Admitted.	Died.	Per cent.
Males	5,245	1677	31.97
Females	6,353	1839	28.94
	11,598	3516	30.31

The following table shows the mortality, *according to sex*, of 1000 consecutive cases of diphtheria observed by Lennox Browne:

Sex.	Admitted.	Died.	Per cent.
Males	533	162	30.39
Females	467	121	25.91
	1000	283	28.30

The following table shows the mortality, *according to sex*, of all cases of diphtheria treated in the Philadelphia Hospital for Contagious Diseases, from 1893 to 1902, inclusive:

Year.	Males.			Females.		
	Admitted.	Died.	Per cent.	Admitted.	Died.	Per cent.
1893	94	29	30.75	123	33	26.82
1894	214	81	37.85	251	73	29.08
1895	315	83	26.40	391	107	27.30
1896	424	100	23.58	445	90	20.22
1897	636	147	23.11	659	153	23.21
1898	562	152	27.04	667	145	21.73
1899	641	139	21.68	732	136	18.57
1900	669	151	22.56	698	147	21.06
1901	416	94	22.59	473	80	16.91
1902	285	64	22.45	316	73	23.10
	4256	1040	24.43	4755	1037	21.80

[1] Browne, Lennox: Loc. cit.

Race.—Race seems to exert no influence over the death-rate from diphtheria. At least this is true in regard to the white and colored patients. Some observers believe that the blacks are more liable to perish from the disease than the whites, but this is not in accordance with our experience, as the following table shows:

Year.	White.			Black.		
	Admitted.	Died.	Per cent.	Admitted.	Died.	Per cent.
1893	208	60	28.84	9	2	22.22
1894	434	144	33.18	31	10	32.26
1895	660	178	26.90	46	12	26.00
1896	838	183	21.83	31	7	22.58
1897	1217	281	23.08	78	19	24.35
1898	1177	289	24.55	52	8	15.35
1899	1304	262	20.09	69	13	18.84
1900	1309	286	21.84	58	12	20.68
1901	843	163	19.33	46	11	23.91
1902	567	129	22.75	34	8	23.52
	8557	1975	23.08	454	102	22.46

While it is impossible to predict at the onset of diphtheria the ending of any case, yet it may be said that when the inflammation of the fauces is mild and the pseudo-membrane not extensive, with but moderate swelling of the lymphatic glands of the neck, the termination is usually favorable. When the exudation is limited to the tonsils the danger is not great; the vast majority of such cases recover without any untoward after-effects. On the other hand, if the inflamed surface be extensive, the pseudo-membrane copious, the exhalations offensive, and the neighboring lymphatic glands and the adjacent tissue very much swollen, the patient's condition becomes perilous. It may be safely asserted that the danger is increasingly grave in proportion to the extent of surface involved and the copiousness of the exudation. The parts implicated in the diphtheritic process must also be taken into account in forming a prognosis. In Lennox Browne's analysis of 1000 cases of the disease the mortality, according to the site of the exudate, was found to be as follows:

Site of membrane.	Cases.	Deaths.	Per cent.
Fauces (alone)	666	81	12.16
Larynx (alone)	4	1	25.00
Nares	2	1	50.00
Fauces and larynx	112	51	45.53
Fauces and nares	165	106	64.24
Fauces, larynx and nares	49	30	61.22
Membrane involving buccal cavity and lips	6	2	33.33
Membrane involving hard palate	12	11	91.66

If the fauces alone are involved the patient has a fair chance of surviving the attack. But where the exudate forms in a thick mass on the hard and soft palates the danger becomes imminent. Sometimes, however, the membrane peels off quickly, leaving the parts

quite free from ulceration, and recovery speedily follows, although paralysis, more or less marked, of the palatine muscles, is rarely absent. The chief source of danger in such cases is from the absorption of the toxins, giving rise to toxemia and heart failure.

When the nares are involved the prognosis should always be guarded. Very many if not the majority of the milder cases of nasal diphtheria recover, and also some of the severe ones. But it is not often that the disease is limited to the nares. If the nasal cavities show distinct plugs of exudate in conjunction with marked faucial involvement, as is usually the case, the child's condition should be viewed with grave apprehension. The foregoing table shows that the mortality from faucial and nasal diphtheria was as high as 64.24 per cent.

In the severe cases of diphtheria nasal involvement is commonly present. As the capillary bloodvessels are very superficial in the cavities of the nose, the slighest congestion or ulceration of the mucous membrane of this part is liable to give rise to troublesome hemorrhage. This of itself is sometimes a source of danger. But the greatest danger is from systemic poisoning, which is extremely liable to occur, since the lymphatics, which are very numerous in the submucous connective tissue of the nostrils, take up the toxins and convey them to every part of the system. This condition always involves great danger of death by asthenia, due to toxemia and heart failure. If recovery takes place more or less paralysis, local or general, is quite sure to develop during convalescence.

The occurrence of middle-ear disease as the result of diphtheria is deemed of sufficient importance to warrant prognostic consideration. It is believed that the diphtheritic process not infrequently extends from the postnasal space through the Eustachian tube to the middle ear. The aural involvement may impair the hearing, but only in rare instances does it result in deafness. Likewise, in severe nasal diphtheria the infection may be conveyed through the cribriform plate to the brain, causing meningitis. In analyzing his 1000 cases of diphtheria Lennox Browne says: "It may also here be mentioned that in one case of nasal diphtheria death ensued from meningitis, and no aural complication was to be found. This circumstance offers a not improbable explanation of the gravity of nasal diphtheria. For, not only do the turbinals constitute an extensive and readily absorbent surface, but there is a liability to direct cerebral infection through the cribriform plate, as has been observed in regard to cerebrospinal meningitis in which the specific organisms have been found in the anterior meninges."

On the first or second day of diphtheria there is but little to be learned from the subjective symptoms that is of prognostic value. A little later, in the graver forms of the disease, one may often seen in the facial expression of the patient something indicating the serious nature of the malady that presents itself for treatment. This appearance has been characterized as a "peculiar facial cachexia." The face

is pale and sallow, often puffy, bloated, or slightly edematous; the skin is smooth and shiny, a muco-purulent discharge issues from the nostrils, the facial outline is somewhat changed by the swelling of the neck, the eyes are clear and bright, but the expression is often that of indolence and apathy. When the attack is likely to prove fatal the face becomes livid or of a dusky, pallid hue; in case of nasal involvement blood may either ooze or flow freely from the nares, and, in malignant cases petchiæ or ecchymoses may appear, not only on the face, but also on other parts of the cutaneous surface. Altogether the facial expression is that of profound blood poisoning, and death may be expected at any moment.

Only in the mildest forms of toxemia is recovery possible. When the patient suddenly becomes extremely pale, vomits everything that is swallowed and the first sound of the heart is found to be diminished in intensity or absent, and the pulse becomes feeble, slow and irregular, or disappears entirely at the wrist, the fatal end is not far off. Often the little patient will utter a shriek, as if suffering from pain, and place his hand over the precordial region just as he is about to expire. In these cases death results from asthenia or heart failure, due to profound systemic intoxication. When diphtheria terminates in this manner it is usually in the second week of the illness.

Temperature.—The prognostic significance of the temperature has been, we think, overrated by most writers. With Lennox Browne we feel that "One is so accustomed to read and hear of the fever of diphtheria that we almost hesitate to declare our conviction—formed on personal observation and confirmed by others whose experience is much greater—that as regards fever there is little to speak of as compared with the acuteness of the constitutional disturbance characteristic of the disease."

If the temperature continues high after the first few days of the illness it is most probably due to the development of some complication. In the worst cases of diphtheria the temperature soon falls to near the normal point, and, as the disease progresses, often becomes subnormal. With the other symptoms of toxemia present, the occurrence of algidity should be regarded as a fatal omen, as it indicates the approach of death as asthenia. In septic cases the temperature may continue high, or it may fluctuate as in most other septic conditions. This can readily be explained by the inflammation of the lymphatic glands of the neck which always accompanies this form of the disease. The prognosis in this variety of diphtheria should be exceedingly guarded.

Pulse.—By carefully studying the pulse from time to time one may sometimes acquire information of considerable prognostic value. So long as the pulse is not too rapid, remains regular and of normal volume, the case is probably progressing favorably. But when it becomes very rapid and feeble, or slow and irregular, our gravest apprehensions

should be aroused. The pulse-rate as well as its volume is influenced more by the absorbed toxins than by the pyrexia.

A rapid pulse within certain limits is not necessarily unfavorable so long as it remains regular. But if it constantly grows more and more rapid, and becomes irregular in its rhythm and force the prognosis is proportionately bad. If, with a frequent and compressible, or a low and intermittent pulse, there is also subnormal temperature, a pale, puffy, apathetic and cachectic face, the prognosis becomes most grave. In speaking of the prognostic value of the pulse in diphtheria, Sir William Jenner says: "An extremely rapid and feeble pulse is of grave import; a very infrequent pulse is of fatal significance."

This disturbance of the circulatory system means that the heart's function is affected by the action of the toxin on the cardiac nerves, and possibly also that the myocardium is undergoing some change through the influence of the poison. When the heart's action becomes slow and weak there is danger of clots forming in the ventricles or in the large bloodvessels connecting with the heart.

Larynx.—One of the special dangers to be feared in diphtheria is involvement of the larynx, giving rise to membranous croup. The disease may occur primarily in the larynx, but more often it begins in the fauces and extends into the larynx. The patient cannot be considered free from danger of the pseudo-membrane extending into this part so long as the disease continues, but the liability of such an occurrence progressively diminishes after the first week.

The danger in membranous croup is twofold: (1) From laryngeal obstruction, causing suffocation and death; and (2) from bronchitis or bronchopneumonia. Much may be done toward overcoming the first source of danger by operative measures, but even then the diphtheritic inflammation too often extends downward into the trachea, bronchi and bronchioles and not infrequently into the alveoli of the lungs, giving rise to bronchopneumonia. We believe that about one-half of the deaths we have seen in membranous croup resulted from the latter complication.

The prognosis may be favorably influenced to a considerable extent by promptitude in employing such measures as intubation or tracheotomy for relief of the laryngeal stenosis. If, after either of these procedures, the child continues to breathe easily and noiselessly, sleeps quietly, takes nourishment well, runs a temperature of not more than 1° or 2° F. above normal, and has a good color, the chances of recovery are favorable. On the other hand, if the respirations are uneasy and noisy the temperature continues high, a troublesome cough with rales throughout the lungs appear, and the color of the patient shows that the blood is not properly decarbonized, the chances of recovery are slim.

Membranous croup is much less liable to be attended by toxemia or followed by general paralysis than are most other forms of diphtheria.

But these affections may occur in cases of membranous croup as the result of involvement of the fauces or nares synchronously with the larynx.

Renal Complication.—Renal complication is not often of much prognostic importance. The slight amount of albumin that is frequently present in the urine is of no great significance, provided that granular and hyaline casts are absent. But when these, together with a large amount of albumin, are found, and the amount of urine excreted is greatly diminished, the outlook is not encouraging. If suppression of the urine occurs, death from convulsions and coma, as the result of uremic poisoning, would soon follow if relief were not promptly afforded. In our experience such a termination in diphtheria is rare.

The prognosis of diphtheria should be greatly qualified when it occurs coincidently with or as a sequel to some other infectious disease, like *scarlet fever or measles*. In patients suffering from the latter disease diphtheria seems especially liable to assume the form of membranous croup, probably because of the catarrhal affection of the larynx usually present in measles. In the year 1900 measles of a malignant type broke out in the diphtheria wards of the Philadelphia Hospital for Contagious Diseases, and the mortality assumed unduly grave proportions. Of 68 cases of diphtheria complicated with measles, 34 died, a death-rate of 50 per cent. Indeed, any independent affection, however mild ordinarily, supervening on an attack of diphtheria may become inordinately severe in consequence of the changed condition of the blood and nervous system of the patient.

Diphtheritic Paralysis.—The danger from diphtheritic paralysis depends very much on the parts involved. So long as the vital organs of the body remain unaffected the prognosis is not unfavorable. Paralysis of the soft palate, however inconvenient it may be to the patient, is not fatal. Likewise, in the average case of multiple paralysis recovery may be expected. Even in the more extreme cases, if the heart's function and the respirations are not affected, the chances of recovery are fair, provided the patient receives proper attention during the critical period. When deglutition is impossible life may be preserved by feeding the child through an esophageal tube. Cardiac paralysis, which is most to be feared, often develops suddenly and gives rise to dangerous symptoms of heart failure. It is liable to occur either early or late in the disease.

We have already mentioned the fact that multiple paralysis does not make its appearance until the fourth to the sixth week of the illness. This complication, as well as some others to which attention has been called, tends to keep the patient's life in danger for a long time. Even when a well-marked case of diphtheria is progressing favorably it is not too much to say that the danger period is not passed, until at least six weeks have elapsed since the beginning of the attack.

CHAPTER XV.

THE PREVENTION OF DIPHTHERIA.

SUSCEPTIBILITY AND IMMUNITY TO DIPHTHERIA.

It is generally well known that not all persons exposed to diphtheria, even by intimate contact, develop the disease; likewise not a few persons carry in their upper air passages diphtheria bacilli possessing a high degree of virulence, as shown by the guinea-pig inoculation test or by the infection of other persons with whom they come in contact, and yet show no clinical evidences of diphtheria. Occasionally individuals possessing this high degree of natural immunity to diphtheria may show in the tissues of the throat localized areas of superficial necrosis produced by virulent diphtheria bacilli, but escape the effects of toxemia and the production of the typical lesions of the disease.

Doubtless various local factors of resistance of the tissues of the nose and throat afford some degree of protection, but it is now known that the chief factor of defense is the presence of natural antitoxin in the blood.

Infants under one year of age are generally immune and known to escape diphtheria even when intimately exposed; in Philadelphia the incidence of the disease at this age is about 3 per cent, so that the immunity is not absolute, but at least 85 to 90 per cent are known to possess antitoxic immunity which, presumably, is inherited from the mother. This immunity, however, gradually disappears, so that at the age of two years the majority of children are susceptible, and the highest percentage of cases of diphtheria develop in children from two to five years of age.

After twelve years of age immunity to diphtheria is gradually acquired by the majority of human beings so that at adult age from 80 to 90 per cent are immune, the incidence of diphtheria in Philadelphia in individuals over eighteen years of age being in the neighborhood of 10 to 12 per cent. This immunity is probably due in part to the acquisition of a greater local resistance of the tissues in the nose and throat as compared with local resistance during childhood; also to the development of a natural antitoxin immunity probably the result of numerous minor infections with diphtheria bacilli capable of stimulating the production of antitoxin without producing well-defined clinical evidences of infection.

Aside from the purely local factors of resistance to diphtheric infection of mucous membranes, antitoxin in the blood constitutes the chief means of defense; von Behring has determined that the presence of approximately $\frac{1}{30}$ unit per cubic centimeter of blood serum will

protect a human being or guinea-pig against diphtheria. This antitoxin in the blood apparently neutralizes the toxin produced by virulent diphtheria bacilli and thereby prevents the necrosing influence of toxin upon the tissue cells with which the bacilli have come in contact; it also neutralizes the toxic absorbed in the lymphatic and vascular channels and thereby prevents toxemia and constitutional reactions.

Antitoxin, however, is not directly inimical to the diphtheria bacilli, but only to its exogenous poison; for this reason it does not directly destroy diphtheria bacilli and the latter may be present in the tonsils or other tissues with relatively large amounts of antitoxin in blood. The bacilli are probably largely destroyed by leukocytes, but antitoxin facilitates leukocytic destruction by neutralization of the toxins; in this manner the administration of horse-serum antitoxin is accompanied by gradual disappearance of the necrotic exudates and bacilli.

THE SCHICK TEST.

For practical purposes tests for antitoxin in the blood serum have proved satisfactory for detecting immunity to diphtheria. Schick[1] has discovered that if human beings are injected *intracutaneously* with $\frac{1}{50}$ the minimal lethal dose of toxin for guinea-pigs and no reaction follows, sufficient antitoxin is present in the blood to confer immunity. This Schick test has been employed extensively during the past fourteen years, and *when properly conducted* has demonstrated its reliability and practical value.

In addition to this direct or clinical test for antitoxin immunity, it is possible to determine the presence or absence of antitoxin in blood serum by mixing serum and toxin together and after a suitable interval injecting a portion of the mixture into guinea-pigs subcutaneously or intracutaneously to determine if the toxin has been neutralized. Under proper technical conditions the dose of toxin is such as will produce necrosis at the site of injection unless neutralized and only diphtheria antitoxin in the serum being tested will effect neutralization. Kellogg[2] has recently advocated this test for practical use in place of the Schick test.

The Toxin for the Schick Test. The proper preparation of the toxin is one of the most troublesome features of the Schick test. The actual amount to be injected *intracutaneously* may vary from about $\frac{1}{30}$ to $\frac{1}{50}$ the minimal lethal dose for 8- to 10-ounce guinea-pigs; our own preference is $\frac{1}{40}$ the minimal lethal dose.[3] These amounts of undiluted toxin are too small in bulk for injection, so that it is necessary to dilute with sterile saline solution. Schick uses 0.1 cc. of diluted toxin, and the writers have always preferred this amount as being less painful, less likely to produce trauma and just as accurate as the injection of 0.2 cc.

[1] München. med. Wchnschr., 1913, **50**, 2608.
[2] Jour. Am. Med. Assn., 1922, **78**, 1782; Am. Jour. Pub. Health, 1925, **15**, 868.
[3] Am. Jour. Dis. Child., 1915, **9**, 189.

The toxin must be potent and active and the amount injected neither too large (which may produce severe local reactions with necrosis) or too small (which may yield falsely negative reactions). The diluted toxin does not keep well and deteriorates within forty-eight to seventy-two hours; for this reason the toxin must be dispensed undiluted and diluted with saline solution just before injection. This insures against deterioration of toxin, greater accuracy in dilution is obtainable and the expense is only slightly greater; for these reasons the bulk toxin is preferable when a number of tests are to be made in hospitals and other institutions.

The Control Fluid for the Schick Test.—In conducting Schick tests on individuals over six years of age it is advisable to include a control fluid in order to detect and properly interpret pseudo or falsely positive reactions and combined pseudo and true positive reactions. These pseudo-reactions are produced in a large degree by the autolyzed protein of the diphtheria bacillus present in the culture broth and not removable by filtration; they will be described in more detail a little later on in this section.

For the purpose of checking these reactions Zingher[1] recommends the use of the same toxin as employed for the Schick test, but heated to 75° C. for ten minutes which destroys all of the toxin and only a slight amount of the autolyzed protein. After heating the toxin the primary dilution is made as described for the unheated toxin.

Method of Conducting the Schick Test.—As previously stated, the *diluted toxin is injected intracutaneously* and *not* subcutaneously. The dose is either 0.1 or 0.2 cc., according to the dilution which is always stated in the directions accompanying the outfit. Moshage and Kolmer tried a cutaneous test by applying undiluted toxin to an abrasion of the skin as in the technique of the cutaneous tuberculin test; reactions occurred after twenty-four and forty-eight hours, but these were seldom as definite and clear cut as the Schick test.

A good syringe and a fine needle are absolutely indispensable. The writers use and can strongly recommend the 1-cc. Record syringe divided in tenths and equipped with a tightly-fitting gauge No. 26 needle. The tuberculin syringe is also useful; it is essential that the syringe work properly without leakage so that an accurate and measured amount may be injected.

The toxin is injected into the skin of the right arm either below the elbow or about the insertion of the deltoid muscle; the control fluid may be injected in the same location on the left arm, but this injection may be omitted in children less than six years of age.

The skin should be cleansed with alcohol, picked up between the thumb and forefinger of the left hand, the needle inserted very superficially with the eye upward, so that the operator may be sure that the needle is introduced far enough and the injection given (Fig. 135).

[1] Am. Jour. Dis. Child., 1916, **11**, 269.

The injection is accompanied by a slight stinging pain and leaves a raised anemic spot, showing the pits of the hair follicles. If this elevated area is not produced the injection has been too deep and should be repeated.

If one syringe is used it is better to inject the control fluid first and then the toxin, in order to make sure that none of the latter is carried into the control injection.

If more than one test is to be given the same needle may be used for all being wiped off with alcohol or 1 per cent iodine solution between

FIG. 135.—Method of administering an intradermal injection. The skin has been cleansed with alcohol and pinched up between the thumb and index finger of the left hand; the needle (No. 26) has been entered into the epidermis and 0.1 cc. of fluid injected. Note the anemic area, indicating that the injection has been intradermic. (Kolmer: Infection Immunity and Biologic Therapy, W. B. Saunders Company.)

each injection. With proper assistance it is possible to give several hundred tests in an hour—much less time is required than for cowpox vaccination.

A dressing is not required; the needle puncture is so small that infection does not occur. The writers have never observed or heard of infection due to a properly conducted Schick test.

The readings may be made twenty-four hours later, if necessary, in order to determine whether or not antitoxin is required. If time permits, it is better, however, to wait forty-eight hours, which permits very slight traumatic reactions to subside. When the tests are con-

PLATE XXV

The Schick Test for Immunity in Diphtheria.

A well-marked reaction thirty-six hours after the intracutaneous injection of one-fortieth the minimum lethal dose of a diphtheria toxin diluted to 0.1 cc. The patient's blood contained no antitoxin. The brownish erythematous area with edematous infiltration of the subcutaneous tissues are characteristic of the reaction. (From Kolmer's Infection, Immunity and Biologic Therapy, W. B. Saunders Company.)

(Reprinted from the *Amer. Jour. Dis. Children.*)

ducted in conjunction with toxin-antitoxin immunization in which there is no necessity for haste in reading the reactions, it is better to make a final reading on the fourth or fifth day. With this interval there is no danger of missing the positive reactions; they are likely to be more clearly defined. Furthermore, the pseudo-reactions will have faded to a large degree and the occasional pseudo- and true combined reactions will be more clearly seen and differentiated from the negative pseudo-reactions.

The Negative Schick Reaction and Its Significance.—In a negative reaction there is no redness and no infiltration because the injected toxin has been neutralized by the antitoxin in the blood. If the toxin was potent and the injection properly given a negative reaction indicates that the individual has at least $\frac{1}{30}$ unit of antitoxin per cubic centimeter of the blood serum, which, according to von Behring and Schick and amply confirmed by others, is sufficient to confer immunity against diphtheria. In individuals over two years of age the immunity is permanent, that is, the antitoxin persists in the blood and subsequent Schick tests continue to yield negative reactions. *In children under two years, however, the immunity (negative reaction) may be only temporary because the inherited antitoxin may gradually disappear;* for this reason the Schick test is only of limited value in children under two years of age and may be omitted altogether.

The Positive Schick Reaction and Its Significance.—When the blood contains no antitoxin or less than $\frac{1}{20}$ to $\frac{1}{30}$ unit per cubic centimeter, the injected toxin is not neutralized and acts as an irritant to the skin. In twenty-four hours there is a circumscribed area of hyperemia about the site of injection varying in size from a quarter to a silver dollar and accompanied by distinct edema (Plate XXV). This reaction reaches its height in three to four days and then gradually disappears, leaving a definitely circumscribed scaling area of brownish pigmentation which persists for three to six weeks.

Severe reactions do not occur unless an error has been made and too much toxin injected, in which case the reaction may be quite large and accompanied by some vesiculation. When properly conducted there is no constitutional reaction and no tenderness of the axillary glands.

A *positive reaction indicates susceptibility to diphtheria*, although, of course, by reason of other factors, not all Schick positive individuals contract diphtheria when exposed. A positive reaction in children does not necessarily mean that the individual will be susceptible for life; it would appear that many acquire natural antitoxin immunity during later years, probably by reason of numerous minor infections stimulating the production of antitoxin.

The Pseudo-positive Reaction and Its Significance.—Pseudo-positive reactions, first described by Park, Zingher, and Serota,[1] are especially apt to occur in individuals over five years of age and may be present in as high as 25 per cent of school children and adults.

[1] Arch. Pediat., 1914, **31**, 481.

Park and his associates have explained these reactions on the basis of local anaphylactic reactions in the protein of autolyzed diphtheria bacilli in the broth. Skin tests conducted by Moshage and Kolmer[1] with suspensions of detoxicated diphtheria bacilli (*diphtherin*), have yielded positive reactions of a similar kind, indicating that many individuals acquire anaphylactic sensitization to the diphtheria proteins; these reactions, however, bear no relation to immunity to diphtheria.[2] In addition to this principal cause of pseudo-reactions, we were of the opinion that trauma and non-specific enzyme reactions to the proteins of the broth independent of those contributed by the diphtheria bacilli, may aid in the production of these reactions.[3]

The pseudo-positive reaction can be interpreted occasionally with fair accuracy by the trained observer from the true positive reaction; but there is usually some doubt as to the absolute certainty of such a reading unless the control injection of heated toxin has been given on the other arm for comparison. The pseudo-positive reaction develops earlier, within six to eighteen hours, reaches its height in thirty-six to forty-eight hours, and is characterized by a central area of dusky redness about the size of a dime, with a characteristic secondary palish areola that shades off into the surrounding skin, and slight or no edema (Plate XXVI, Fig. 1). After fading it leaves none, or but very slight, pigmentation and scaling of the skin.

Occasionally, and especially among adults, a *combined true and pseudo-positive reaction* may be seen. The central area of brownish redness is larger and accompanied by *distinct edema*; this is surrounded by the same palish erythema as seen in the pseudo-reaction (Plate XXVI, Fig. 2). Definite brownish discoloration and scaling of the skin follows as in the true reaction (Plate XXVI, Fig. 3). If heated toxin has been injected as a control, a typical pseudo-reaction will be observed and the development of these control reactions indicate that special caution is necessary in reading and interpreting the reactions excited by toxin. When in doubt, it is better to regard the toxin reaction as a true positive and err if necessary on this side.

The Pseudo-reaction in Relation to Toxin-antitoxin Immunization: The Necessity of a Control. Zingher[4] has recently emphasized that children yielding pseudo-Schick reactions are most likely to develop pronounced local and constitutional symptoms after injections of toxin-antitoxin. This is to be expected when it is remembered that the pseudo-reaction is principally due to sensitization to the proteins of the diphtheria bacillus contained in the toxin broth. For this reason the control injection is always advisable, indeed, is almost a necessity, in Schick tests on individuals over five years of age and especially of toxin-antitoxin immunization is to be given; by means of the control injection the pseudo-reactions are readily detected and given special attention in active immunization. The control injection also aids in the interpretation of combined pseudo- and true Schick reactions; in such

[1] Am. Jour. Dis. Child., 1916, **12**, 316.
[2] Jour. Immunol., 1916, **1**, 334.
[3] Jour. Am. Med. Assn., 1915, **65**, 144.
[4] Ibid., 1922, **78**, 1945.

PLATE XXVI

A Fading Schick Reaction Showing Brownish Discoloration and Fine Desquamation.

A Pseudopositive Schick Reaction.

A Combined True and Pseudopositive Schick Reaction.

(From Kolmer's Infection, Immunity and Biologic Therapy, W. B. Saunders Company.)

individuals the first dose of toxin-antitoxin should be about one-half that ordinarily given (0.5 cc.) in order to reduce the degree of reaction that may follow.

The Percentage of Positive Schick Reactions and the Influence of Age, Race and Inheritance.—The percentage of positive reactions at different ages reported by different investigators, and even by the same investigators at different times, have varied to a considerable degree. Doubtless these variations have been largely due to defective toxin (too much, too little, or inactive), errors in injection and interpretation of results; also according to locality (urban or country districts), race and social condition, and general health. For example, Zingher[1] has observed in New York City a much higher percentage of positive Schick reactions (as high as 75 per cent) among school schildren from the homes of the more well-to-do than those from the homes of the poorer classes living in closely crowded neighborhoods (as low as 16 to 20 per cent), where the chances of contact infection and the development of natural immunity are greater. An unusually low proportion of positive reactions occurred among the children of Italian parents.

An exception to this general rule was noted among colored children, the percentage of positive reactions being high despite the fact that the majority lives in congested districts. Wright,[2] however, observed about the same percentage of positive reactions among adult negroes as white adults.

Park, Zingher, and Serota also found a marked tendency for all children of the same family to show a similar Schick reaction, whether it was positive or negative. Where variations occurred the younger children, as a rule, gave a positive reaction and the older children a negative; the reverse condition was very rare, except in families with young infants, who often gave a temporary negative reaction due to inherited immunity.

Bearing in mind these modifying factors, it is almost useless to attempt expressing the percentage of positive Schick reactions at different ages; 52,000 tests conducted by Zingher among the school children of New York, varying in age from six to fifteen years, or thereabouts, have shown positive reactions varying from 13.6 to 67 per cent and pseudo-reactions varying from 3.9 to 26 per cent. Figures, however, will indicate in a general way the influence of age and may be given as follows:

	Per cent, positive.
1 to 6 months	15
6 to 12 "	50
1 to 2 years	55
2 to 4 "	65
4 to 6 "	40
6 to 8 "	35
8 to 20 "	25
20 to 40 "	18
Over 40 "	12

[1] Jour. Am. Med. Assn., 1921, **77**, 835.
[2] Jour. Infect. Dis., 1913, **21**, 265.

The Influence of Disease Upon the Schick Reaction.—In 1915 Moshage and Kolmer[1] called attention to the higher percentage of positive Schick reactions occurring among persons with scarlet fever. Zingher[2] observed that the reactions were twice as frequent in this disease, slightly more frequent during measles and nearly three times as high during poliomyelitis. Lereboullet,[3] however, did not find that measles influenced the reactions.

The Relation of the Schick Test to Diphtheria Carriers and to the Diagnosis of Diphtheria.—There is no relation between the percentage of carriers of diphtheria bacilli and the Schick reaction. An individual may carry virulent bacilli in the nose and throat without evidences of diphtheria and yield a negative Schick reaction, because of the presence of sufficient antitoxin in the blood to protect against that produced by the bacilli and to neutralize that injected into the skin. As previously mentioned, however, Park has observed that virulent diphtheria bacilli may produce some inflammatory changes in the tonsils with superficial necrosis in Schick-negative individuals; this indicates that the bacilli and their toxins may produce some tissue changes when so superficially located as to be beyond the neutralizing influence of antitoxin in the blood.

Individuals may carry diphtheria bacilli and yield positive Schick reactions. In the majority of such cases the bacilli are found non-virulent for guinea-pigs. For this reason the Schick test is of some aid in the managment of cases showing diphtheria or diphtheroid bacilli in nasal and aural discharges; if the Schick reaction is positive it indicates that the bacilli are very probably non-virulent, for the skin reaction indicates the absence of antitoxic immunity in which case the patient would probably show clinical evidences of diphtheria if the bacilli were virulent. We have observed, however, positive Schick reactions among diphtheria convalescents harboring virulent bacilli; doubtless there are other local tissue and immunity principles that may protect an individual against virulent diphtheria bacilli even though lacking in antitoxic immunity.

The Schick test, therefore, is not a substitute for the culture method in the diagnosis of diphtheria and the detection of carriers. It aids, however, in the management of carriers as discussed above. The test is not an index of the virulence of bacilli recovered in cultures; the guinea-pig inoculation test is the only reliable one for this purpose.

The Practical Value of the Schick Test.—A large number of investigators have found the Schick test safe and a reliable and simple means for determining the presence or absence of immunity to diphtheria. Accidents have happened, severe reactions have been produced by the injection of too much toxin; likewise a few have claimed that diphtheria developed among those yielding negative reactions, but the great bulk

[1] Am. Jour. Dis. Child., 1915, **9**, 169.
[2] Ibid., 1917, **13**, 247.
[3] Bull. et mém. Soc. méd. d. h_p., 1921, **45**, 1210.

of evidence is favorable to the test and indicates unmistakably that when *properly conducted* the test is without danger and of much value.

Unfortunately, the practical application of the test is hampered by the chances of using defective toxin and the necessary procedures for diluting and injecting it; also by the occurrence of pseudo-reactions, but these difficulties soon disappear with a little experience and especially when bulk toxin can be used as required for a large number of tests in schools, hospitals and other institutions.

The test has its greatest value as a means for detecting those lacking in antitoxic immunity and requiring immediate protection by an injection of antitoxin when exposed to diphtheria or, in the absence of acute exposure, slower but more lasting immunization by toxin-antitoxin or toxoid mixtures. By means of this test a large number of individuals may be spared the discomfort and useless sensitization caused by injections of horse-serum antitoxin, and it has given great impetus to active immunization with toxin-antitoxin and toxoid mixtures.

The *influence of age upon the reaction* is to be remembered, that is, that a child under two or three years of age may react negatively and later positively, when its inherited immunity has disappeared. For this reason young children should be retested at intervals to detect susceptibility should such develop. After four or five years of age the reaction is greatly stabilized, that is, continues to yield negative reactions probably for life, or positive reactions, unless the individual is immunized.

It is not necessary, however, to use the test on children under five years of age in relation to toxin-antitoxin immunization; the majority give positive reactions anyhow, and the Schick test may be omitted in this group and toxin-antitoxin given to all children between six months and five years. After six years of age, however, the Schick test and its control should be conducted.

Naturally the test has its greatest usefulness under conditions where the spread of diphtheria is facilitated, as in the wards for children in hospitals, in institutions for children and adults as well, among nurses, physicians and others brought in contact with diphtheria or diphtheria carriers. Cooke and others have shown the value of the test among nurses and immunization of susceptibles by injection of toxin-antitoxin mixtures. In our opinion the Schick test should be conducted routinely under these circumstances and the positive reactors either actively immunized with toxin-antitoxin mixtures or passively with antitoxin, when intimately exposed.

In private practice physicians will do well to acquaint parents with the advantage of the Schick test and active immunization and to encourage their use. By grouping individuals in private practice a number of tests may be done in one day, thereby minimizing the work involved.

It is very much hoped that state and city departments of health will facilitate the application of the Schick test and active immunization

by providing suitable outfits and even trained physicians for conducting the tests, especially in institutions and schools. The work being carried out in the schools of New York City consisting in conducting the Schick test and actively immunizing the positive reactors, should be closely followed, as it bids fair to prove a useful and practical means for really reducing the incidence of diphtheria.

SERUM PROPHYLAXIS OF DIPHTHERIA.

The subcutaneous administration of relatively small doses of antitoxin will usually confer a passive immunity against diphtheria lasting from two to four weeks.

The *object* is to introduce antibodies (antitoxin and opsonin) into the body fluids in order that they may neutralize the toxin as rapidly as it is produced, aid in the destruction of the bacilli, and thus protect the individual in case virulent bacilli should be inspired or otherwise gain access to the tissues.

Although the value of antitoxin in the management of diphtheria is no longer debated and its use has come to be almost universal in the treatment of the disease, medical opinion seems to be divided as to the desirability of employing the antitoxin as an immunizing agent when persons are exposed through contact with infected patients. There is always some risk of immediate or remote consequences of a disagreeable and possibly of an alarming or dangerous nature, so that the clinician will naturally weigh this possibility before subjecting a healthy person to whatever danger may be involved in the immunizing procedure. The best statistical record of deaths from antitoxin shows 1 death among approximately 75,000 persons injected. The alternative that is advocated *in lieu* of prophylactic antitoxin is a careful examination of the contacts each day by a physician and the use of therapeutic doses of antitoxin at the earliest indication of clinical infection. While this cannot be expected to diminish the risk of infection, it should lessen the risk of death. Such attempts to avert a calamity are not free from serious difficulties, and the least of which are the uncertainties of early diagnosis and the continued careful surveillance demanded. Added to this, furthermore, is the risk of death from diphtheria if it should be contracted by an exposed person. From a practical standpoint, the statistics recently gathered at Baltimore by Doull and Sandidge are quite significant. According to their records of more than 500 consecutive cases of diphtheria, 10 per cent of the family contacts of ten years and under who were not given prophylactic antitoxin subsequently developed diphtheria, mostly within thirty days. Of the children of the same group who were given prophylactic antitoxin, only 1.2 per cent were attacked. This experience, the authors state, is in agreement with the experience of other writers with regard to the low secondary attack-rates among

immunized children and the very much higher rates among children not so treated. These findings demand serious consideration in the debate as to whether dependence should be placed solely on frequent examination of the throats of contacts and the administration of sufficient doses of antitoxin therapeutically in case of developing diphtheria rather than on the prophylactic use of the antitoxin when infection is threatened by environmental circumstances.

Dosage and Administration.—The *doses* advised are relatively small, and the injection does not usually produce any discomfort other than soreness about the site of inoculation. For infants under one year of age 500 units suffice; for older children and adults from 1000 to 1500 units should be given. Antitoxin has been administered orally, but the results are irregular and the degree of immunization inconstant; for these reasons the serum should be given by subcutaneous injection.

Duration of the Immunity.—The *duration of this passive immunity is relatively short,* owing to the fact that the antitoxin is eliminated rapidly, as it is part and parcel of a foreign serum that tends to be excreted or destroyed soon after its introduction into the body. It will endure, however, for at least two weeks, and frequently two to four weeks longer. Since the incubation period of diphtheria is only a matter of a few days, this suffices, in the majority of instances, to protect the individual. But if the danger of infection lasts for more than six weeks a second injection may be required.

Indications.—The indications are to immunize all persons who have come in intimate contact with a case of diphtheria. *If time permits the Schick test should be conducted, as only those persons yielding positive reactions require the antitoxin.* It is especially valuable in families and small communities, such as go to make up hospital wards and asylums. The physician who is attending a case of diphtheria in a private home should urge immunization upon all members of the household who have been exposed to infection.

The Schick Test in Relation to Passive Immunization Against Diphtheria.—As previously stated, only those persons showing a positive Schick reaction require immunization when exposed to diphtheria because of susceptibility to the disease. Children over two years and adults who have yielded negative Schick tests *properly* conducted do not require immunization because they are immune to the disease probably for life. For this reason the Schick test is particularly valuable to physicians, nurses and others especially likely to be exposed in diphtheria; if known to be Schick-negative the administration of antitoxin is not required.

When time permits the Schick test may be conducted before antitoxin is injected on a large scale to *adults,* as inmates of a ward or institution; this delays the injection of antitoxin, but in our opinion is justifiable, as the majority of adults are immune and will yield negative reactions. With *children,* however, from two to twelve years of age, this delay may not be advisable if there is reason to believe that they

have been intimately exposed, because the majority are susceptible to the disease and yield positive Schick reactions.

Results.—The *immediate results* are usually good. The main disadvantage is the short duration of the immunity, so that no matter how faithfully it is carried out, persons do not remain immune for long periods of time, and accordingly the total morbidity of the disease is not influenced to any extent. In homes from which the case of diphtheria is promptly removed to a special contagious hospital and in which the remaining members are promptly immunized the percentage of secondary cases is practically *nil*. Of 6772 patients who were removed to the Philadelphia Hospital for Contagious Diseases, the remaining members of the family not being immunized, secondary cases developed in 164 persons, or in 2.4 per cent. Of 4063 cases of diphtheria treated at home with antitoxin, the other members of the family not being immunized, secondary cases developed in 219 persons, or in 5.3 per cent. Of 639 diphtheritic patients treated at home who did not receive antitoxin and where immunization was not practised, secondary cases developed in 151 persons, or 23.6 per cent. These figures, compiled from the annual reports of the Philadelphia Bureau of Health, for the years of 1909, 1910 and 1911, show that the best results are obtained when the diphtheritic patient is promptly removed to a special hospital and the remaining members of the household are immunized. Similar results have been reported by Braun,[1] who found that only 1.62 per cent of a group of 2218 children exposed to diphtheria and immunized with serum developed the disease, whereas nearly 35 per cent developed diphtheria in families not immunized. Even when the patient is removed promptly there is some danger of other members of the household, even if immunized, developing the infection, probably owing to the fact that the patient harbors virulent bacilli for varying periods of time after the passive immunity in other persons has passed away and the quarantine is broken. Certainly in those homes where antitoxin is not used either for therapeutic or for prophylactic purposes, the percentage of secondary infections is so high as to leave no doubt as to the value of antitoxin.

In this connection we may mention the desirability of using an antitoxin prepared by immunization of cattle for the general purpose of prophylaxis, and especially for the treatment of those persons who are hypersensitive to horse serum. In these cases horse antitoxin could be used later if a person contracted diphtheria, without danger of anaphylaxis.

TOXIN–ANTITOXIN VACCINATION AGAINST DIPHTHERIA (TOXIN–ANTITOXIN IMMUNIZATION).

Historical. Owing to the fact that the antibodies produced through the activities of our own body cells (active immunization) persist for

[1] Deutsch. med. Wchnschr., 1913, **40**, 1145.

longer periods of time than those that are introduced passively (passive immunization), von Behring and his assistants have developed a method of active immunization in diphtheria whereby our own body cells are stimulated to produce our own antitoxin in sufficient amounts to protect us against the disease. It has long been known that more or less balanced mixtures of this kind produce immunity in animals. Babes, in 1895, was the first to inject experimentally diphtheria toxin-antitoxin mixtures and to appreciate that not only slightly toxic but also that slightly over-neutralized mixtures would engender the production of antitoxin in animals. At about the same time, and independently, Park, of New York, made the same observation, and began to use this knowledge in the immunization of horses for the production of antitoxin. Park noted that the use of large amounts of over-neutralized toxin was a safe and rapid method of beginning immunization of horses; that is, the antitoxin protected against fatal reactions, but yet active immunization occurred because small amounts of toxin became gradually dissociated and served to stimulate the body cells to produce antitoxin. Exactly the same mechanism is operative in the immunization of human beings with these toxin-antitoxin mixtures.

In 1907 Theobald Smith[1] suggested that it might be possible to employ this method for the purpose of producing immunity in man. Subsequently Smith[2] studied the effects of injections of neutral mixtures in guinea-pigs and horses, and again pointed out the applicability of the method to human beings. Finally this was accomplished by von Behring,[3] in 1913, by demonstrating in a few human beings the safety of the injections. Shortly afterward Hahn and Summer[4] injected 1097 children in the district of Magdeburg, where diphtheria was endemic. Of these, 633 received the full series of three injections, 255 received two injections and 209 received one. The Schick test was not employed. For the first two weeks there was no difference in the number of cases of diphtheria in the vaccinated and unvaccinated, but after that time there was a lessening of the number in the vaccinated group. In 1920 Bieber was able to study the histories of the majority of these individuals and reported that during the six years 15 per cent of the unvaccinated group contracted diphtheria, whereas only 4.6 per cent of the vaccinated contracted the disease.

Mechanism of Toxin-antitoxin Immunization.—Active immunization in diphtheria could probably be accomplished by the administration of minute and increasing doses of toxin, but there would be some danger of producing local necroses, an acute toxemia or paralysis, and the process may require so much time as to be useless in the presence of epidemics.

Von Behring's method, according to his report, read before the German Convention on International Medicine in 1913, is based upon

[1] Jour. Med. Res., 1907, **16**, 359.
[2] Jour. Exper. Med., 1909, **11**, 241.
[3] Deutsch. med. Wchnschr., 1913, **39**, 873.
[4] Jour. Am. Med. Assn., 1922, **79**, 1584.

the principle that the union of toxin and antitoxin is not stable, and when a neutral mixture of the two is injected into animals sufficient toxin becomes dissociated to unite with body cells and stimulate the production of antitoxin.

The amount of antitoxin injected does not confer an appreciable immunity; therefore, this method of immunization cannot be regarded as a combined active and passive immunization, but is purely a process of vaccination or active immunization by means of the toxin stimulating our body cells to produce antitoxin.

Formerly immunization was conducted with mixtures of toxin-antitoxin which were slightly over-neutralized or just neutral; at the present time mixtures containing 0.1+ dose of toxin neutralized with the required amount of antitoxin are being employed.

Dose and Method of Administration.—The dose is 1 cc. injected subcutaneously once a week until three doses have been given. For children under one year of age three injections of 0.5 cc. each are given. The injections may be given in the arm at the insertion of the deltoid muscle or under the skin of the abdomen. Zingher has found that two injections of larger amounts (1.5 cc.) do not give as good results as three injections of a smaller amount. In about 5 to 8 per cent of Schick-positive individuals a fourth even a fifth dose may be required to render them immune (Schick-negative).

Age in Relation to Immunization.—Apparently the most favorable age is from six months to two years. According to Park, infants under six months do not usually respond with the production of antitoxin because of the combined effect of immature cells and the over-neutralization of the toxin-antitoxin mixture (due to the presence of natural antitoxin in the blood); the injections, however, produce no ill-effects.

As previously stated, it is scarcely worth while conducting a preliminary Schick test with children six months to two years of age, because if a negative reaction occurs this result may be temporary and misleading and the child lose its immunity later on as the natural antitoxin disappears. Toxin-antitoxin may be given to all, even though it means that a few children may not actually be in need of immunization. With older children and adults the Schick test should be done first, and only the positive reactors selected for immunization.

Children bear the injections better than adults, but immunization may be safely practised at any age; the best time, however, is during early childhood, from six months to six years of age.

Reactions.—Adults and older children may develop local reactions of slight edema, erythema and tenderness, regarded as anaphylactic reactions to the dissolved proteins of the diphtheria bacilli in the toxin. Children under four years commonly do not show any reaction. *Persons who have shown a combined true and pseudo-Schick reaction are especially likely to develop a local reaction*, the latter indicating a hypersensitiveness to the proteins in the toxin. Occasionally a local reaction

is accompanied by slight fever and malaise. According to Park, in children of school age about 10 per cent develop fairly sore arms and temperatures of from 99° to 103° F. About 5 per cent feel miserable enough to stay at home from school for one day, and very few for two days. In adults the reactions are apt to be more frequent and severe, but not quite as marked as follows injections of typhoid-paratyphoid vaccines. In infants the reactions are practically negligible.

Probably some degree of anaphylactic sensitization to horse-serum proteins is engendered by the injection of toxin-antitoxin, but the degree of sensitization is very slight and does not constitute a contraindication to the administration of horse antiserum (like tetanus antitoxin, antimeningococcus serum, etc.) at a later time in life. Steele[1] has reported a case of serum sickness following the administration of toxin-antitoxin, and Hooker[2] has likewise found that a noteworthy proportion became sensitive to horse serum when tested by intradermal reactions. In our opinion great care should be exercised in giving it to horse asthmatics, but otherwise no special precautions are required, although it would appear highly desirable to immunize with toxoid or with mixtures prepared of cattle antitoxin instead of horse antitoxin in order to avoid all possible sensitization to horse serum.

The Development of Immunity.—After each injection a portion of the toxin becomes dissociated from the antitoxin and serves to stimulate the body cells with the production of antitoxin, but the process is slow and generally three or six months are required after the last dose for the production of sufficient antitoxin to render the patient Schick-negative.

According to Zingher, one injection of toxin-antitoxin will immunize about 60 per cent of Schick-positive reactors; two injections immunizes about 80 per cent and three injections about 90 to 95 per cent. By reinjecting those who still give a well-marked positive Schick reaction at the end of three months, with two or three more doses of toxin-antitoxin, an active immunity may be developed in almost all susceptible persons. If the Schick test is only faintly positive one additional injection of toxin-antitoxin will probably suffice.

Duration of Immunity.—According to Park and Zingher, who have had an extensive experience in New York, the immunity after three doses of toxin-antitoxin, prepared as described above, apparently lasts for six years and the indications are that it may persist for a lifetime. A child successfully immunized at four years of age may expect protection at least until twelve to fifteen years of age, at which time natural immunity will probably have developed to such degree as to afford protection for the balance of life. Schroeder[3] found in one series of children that the immunity persisted for five years, and in a second group of 570 children immunity had persisted for at least two years in 90 to 95 per cent. Meyer[4] has observed that immunity has

[1] Jour. Am. Med. Assn., 1924, **82**, 1262.
[2] Jour. Immunol., 1924, **9**, 7.
[3] Arch. Pediat., 1921, **38**, 368.
[4] Jour. Am. Med. Assn., 1922, **78**, 716.

persisted in 94.4 per cent of a group of children for at least forty-four months. It is entirely likely that retesting (Schick) will show that the majority of these children are still immune and that they will continue to yield negative reactions.

Dangers and Contraindications.—When the toxin-antitoxin mixtures are properly prepared extensive experience has shown that the method is without danger. Zingher reports that many thousands of injections have been given with the toxin-antitoxin preparation of the New York Research Laboratory of the Bureau of Health without a single untoward result. Deplorable accidents have occurred due to the injection of mixtures too highly toxic for the guinea-pig and these emphasize the necessity for extreme care in preparing and testing the mixtures. According to Zingher mixtures properly prepared always remain safe, that is, do not acquire increased toxicity and remain effective for immunization for at least six months.

Kelley,[1] however, reported severe local and constitutional reactions in 40 some children injected with mixtures prepared according to the old formula containing one L+ dose of toxin, in which the toxicity was ascribed to the effects of freezing and thawing of the mixtures resulting in the dissociation of toxin. White and Robinson,[2] in an experimental study, found an increased toxicity of at least one mixture of this kind as a result of low temperature changes, but Anderson and Leonard[3] and Kirkbride and Dow[4] found no evidence at all that freezing and thawing increased the toxicity of mixtures prepared by the new and present-day formula carrying 0.1 L+ dose of toxin. As might have been expected, the fanatical elements which constantly agitate against the application of the facts of scientific medicine to the prevention of disease seized this incident, and endeavored to exploit it to the utmost. Their efforts should not, however, cause any one to be deterred from the use of the toxin-antitoxin method for the prevention of diphtheria. Almost a million inoculations in New York without the slightest distress, and hundreds of thousands elsewhere in the United States, should be sufficient evidence as to the safety of the method and as to its desirability.

Von Behring advises against the immunization of atrophic infants and individuals suffering with acute active tuberculosis. The fear expressed by some that immunization is contraindicated in those persons harboring diphtheria bacilli or in the presence of epidemic, by reason of producing a negative phase of temporary depression of resistance, has been finally dissipated by practical experience. Not one of numerous carriers injected with toxin-antitoxin has developed diphtheria. Whether or not active immunization with toxin-antitoxin aids in getting rid of the bacilli is still an open question, but very probably does not have this effect.

[1] Jour. Am. Med. Assn., 1924, **82**, 567.
[2] Ibid., 1675.
[3] Ibid., 1679.
[4] Ibid., 1678.

Practical Value and Recommendations.—Diphtheria still remains an active and widely prevalent disease throughout the world, even though the mortality has been reduced from 70 to 75 per cent to 10 per cent since the advent of antitoxin in 1894. For the United States it is calculated that the yearly incidence of the disease is from 150,000 to 200,000 cases per year and the deaths 20,000 to 22,000 per year. Despite vigorous public health measures and the prophylactic use of antitoxin, the disease demands greater efforts toward its eradication, and for this purporse the widespread use of active immunization with toxin-antitoxin mixtures is proving most valuable.

The mortality-rates of diphtheria per 100,000 in fifteen of our largest American cities from 1890 to 1894 preceding the antitoxin area was 94.13; for the twenty-five years (1895–1919) following the use of antitoxin and preceding toxin-antitoxin immunization it was 32.92, while from 1920 to 1925 it was reduced to 15.39.

In New York City, where approximately 40 per cent of school children have been immunized, the incidence of diphtheria has been reduced from 265 per 100,000 to 183 and the mortality from 24.43 to 8 per 100,000.

Auburn, N. Y., is perhaps the most classic example of what may be accomplished when physicians and laymen coöperate with the health office of the community. It is a unique instance not only because the immunization idea is being given a fair test under practically perfect control, but also because in three years Auburn has not had a single death from diphtheria *in children or adults.*

In spite of the potential peril from the ubiquitous carrier, it is a gratifying fact that the practical value of immunization is usually in geometric rather than arithmetic proportion to the number of persons inoculated.

It is interesting to note that when the incidence has increased apparently "in spite of immunization," almost invariably the cases and the deaths occurred among the non-immunized. However, as immunity is not established with less than three inoculations and two to seven months' time, it would seem logical to commence the process during the low-prevalence seasons, so that when the diphtheria seasons come the number of susceptibles is diminished.

Immunization of school children does not entirely solve the problem. It is the preschool child who stands in greatest danger of getting the disease and of dying from it. *The best age at which to inoculate is from nine to eighteen months.*

It is not too much to predict that another decade or two will see diphtheria at least 85 per cent prevented and at least 90 per cent (of the 15 per cent) cured. It is true that the epidemic and the carrier problem still require elucidation, but serious as these are, the chief obstacles are ignorance, indifference, prejudice and superstition, which all through history have opposed scientific progress. That these factors operate against the prevention of diphtheria is shown by the

observation of public health officers everywhere that their results almost invariably may be measured by the extent of the coöperation offered by the doctors and laymen of the community.

In the presence of exposure to diphtheria when rapid protection is required antitoxin should be injected; the immunity engendered by toxin-antitoxin mixtures develops too slowly for this purpose. It is to be remembered, however, that *antitoxin protects for only a few weeks.*

Physicians, nurses and others especially likely to be exposed to diphtheria should have the Schick test conducted, and if positive, should be immunized with toxin-antitoxin mixtures. This is especially advisable for nurses who may thereby avoid the disagreeable effects of one or more injections of antitoxin during their training and in subsequent practice. It is gratifying to learn that for them, too, there is promise of successful active immunization following the practice of systematic administration of toxin-antitoxin mixtures to those who react to the Schick test. Cooke[1] has reported the outcome of such a program for the susceptible training school nurses on duty in the Contagious Pavilion of the St. Louis Children's Hospital, a group of young women showing an unusually high incidence of susceptibility. There were 58 per cent of non-immunes. More than 80 per cent were immunized by the injections, the Schick test remaining persistently positive after two series of toxin-antitoxin injections in only a small number of the women. During the three years preceding the immunization, 20 nurses, or 28 per cent of those on duty in this contagious pavilion, developed diphtheria. In the four years' period after the immunization was instituted there was a decrease in the incidence of clinical diphtheria among these nurses of at least 90 per cent. This is a triumph of preventive medicine. If it is thus easy to protect an entire nursing staff from contracting diphtheria by the use of the Schick test and toxin-antitoxin injections; one must agree with Cooke that this procedure should be carried out in all institutions caring for children.

Since diphtheria is preëminently a disease of children, it may be said that the Schick test and toxin-antitoxin immunization have proved so reliable when properly administered that all children known to be susceptible to diphtheria should be immunized. This is particularly true of children in institutions, as hospitals and asylums, where close contact increases the incidence, but even in private practice physicians should acquaint parents with the advantage of these procedures and advise their use.

Zingher has demonstrated in the schools of New York City that it is possible to conduct the Schick test and apply toxin-antitoxin immunization on a large scale, and it is very much hoped that other cities and states adopt similar procedures for the solution of the diphtheria problem.

[1] Am. Jour. Dis. Child., 1922, **23**, 496.

The Schick test is a great aid, but may be dispensed with under the following certain conditions:

(*a*) *Infants under six months of age* do not require the Schick test or active immunization, inasmuch as 80 to 90 per cent are immune to diphtheria (presumably inherited from the mother). Furthermore, Zingher has shown that they do not produce antitoxin very well even when immunized.

(*b*) *All children six months to two years of age* should be immunized, as this is the most important period. The Schick test may be omitted because it is not reliable at this age, inasmuch as a child reacting negatively may lose its natural immunity and later react positively.

(*c*) *Children two to five years of age* may first be tested by the Schick test because after two years a negative reaction is reliable, inasmuch as it remains constant. But since the majority of children react positively the Schick test may be omitted as a routine procedure and active immunization applied to all.

(*d*) *Children six to fifteen years of age and adults* should first have a Schick test; toxin-antitoxin immunization is only required when the reactions are positive.

(*e*) Immunity to diphtheria after toxin-antitoxin immunization can never be assumed to have been produced; the only reliable evidence of this is actual demonstration of antitoxin in the blood, and for this purpose the Schick test should be conducted three to six months after the last injection.

TOXOID OR ANATOXIN VACCINATION AGAINST DIPHTHERIA.

The slow development of immunity following toxin-antitoxin immunization, and the few accidents which have followed its use, along with the possibility of producing sensitization to horse serum, has led to attempt vaccination against this disease by injections of toxin modified in various ways to convert it into non-toxic toxoid or anatoxin. The latter term is used in Europe, but "toxoid" would appear to be a better one, since the new word "anatoxin" may be mistaken for antitoxin because they sound so much alike.

It has been known for many years that toxin converted into toxoid by the addition of formalin is capable of producing antitoxin in horses. Indeed, Glenny and Hopkins[1] found that toxoid prepared in this manner was even a better immunizing agent for the lower animals than toxin itself, and that it could be so concentrated that the antigenic power was increased forty-fold with the same nitrogen content.

Ramon[2] states that on adding commercial formalin (35 to 40 per cent) in the concentration of 0.3 to 0.4 per cent at 40° to 42° C. he obtained a product non-toxic for guinea-pigs in dose of 0.5 cc., whereas the toxin itself before treatment was lethal in dose of 0.00125 cc.

[1] Brit. Jour. Exper. Path., 1923, **4**, 283; Jour. Path. and Bacteriol., 1924, **27**, 261.
[2] Ann. d. l'Inst. Pasteur, 1924, **38**, 1.

Horses injected with this toxoid or anatoxin produced as much antitoxin as those that have been injected with toxin.

Park and Zingher[1] and their associates found that toxoid preparations had good immunizing effects with but slight local and constitutional reactions providing the dose did not exceed 0.5 cc. Henseval and Nélis,[2] Darré and his associates,[3] Marie,[4] Ponce de Leon,[5] Nasso,[6] Lereboullet and his co-workers[7] and Flandin[8] have also published very encouraging reports indicating that *immunity is developed more rapidly than with toxin-antitoxin mixtures and with practically no reactions.* The injections are given subcutaneously in two doses of 1 cc. each to children under 8 years, with an interval of three weeks; older children and adults may receive two doses of 0.5 cc. each and a third dose of 1 cc. unless a preliminary skin test with a 1:20 dilution of toxoid yields a negative reaction and thereby indicating an absence of hypersensitiveness.

Zoeller and Manoussakis[9] found that skin tests conducted with toxoid did not give reactions corresponding to Schick tests with toxin. The toxoid reactions were evidently due to the proteins of the diphtheria bacillus and probably similar to those reported by Kolmer and Moshage[10] with *diphtherin* in 1916. Local and constitutional reactions consist of tenderness, induration and redness at the site of injection with malaise, headache and fever, lasting 1 to 3 days; they are rare in children under 8 years of age.

Nélis[11] has prepared toxoid by adding sodium oleate to the toxin, and Larson and Eder[12] have used 0.125 L+ of toxin in 1 cc. of 2 per cent sodium ricineolate, but it is too early to express an opinion of their value as immunizing agents.

However, it would appear that toxoid immunization may supplant toxin-antitoxin immunization if future experience supports present observations indicating that fever doses (usually two of 1 cc. each) are required and immunity more rapidly produced along with fewer local and constitutional reactions. Zoeller[13] states that the results are not only due to the production of antitoxin, but likewise to the acquired property of producing it rapidly when occasion demands in the way of increasing the capacity of an individual for reacting to infection. Furthermore, as reported by Lereboullet and Joánon,[14] the immunity is probably as lasting as that produced by toxin-antitoxin immunization.

[1] Am. Jour. Dis. Child., 1924, **28**, 464; Am. Jour. Pub. Health, 1924, **14**, 1047.
[2] Compt. rend. Soc. de biol., 1924, **91**, 902.
[3] Bull. et mém. Soc. méd. d. hôp., 1925, **49**, 565.
[4] Presse méd., 1925, **33**, 266.
[5] Rev. méd. Latino Americano, 1925, **11**, 607.
[6] Pediatria, 1925, **33**, 1312.
[7] Bull. et mém. Soc. méd. d. hôp., 1926, **50**, 683.
[8] Ibid., 691.
[9] Compt. rend. Soc. d. biol., 1925, **92**, 1290; 1924, **91**, 165.
[10] Am. Jour. Dis. Child., 1916, **12**, 316.
[11] Compt. rend. Soc. d. biol., 1924, **91**, 1159.
[12] Jour. Am. Med. Assn., 1926, **86**, 998.
[13] Bull. et mém. Soc. méd. d. hôp., 1925, **49**, 744.
[14] Bull. et mém. Soc. d. hôp., 1925, **49**, 773.

CHAPTER XVI.

THE TREATMENT OF DIPHTHERIA.

ISOLATION AND SANITARY PRECAUTIONS.

As soon as the nature of the disease is known the patient should be separated as far as possible from the other members of the household. This is important even when the attack is ever so mild, as severe cases may result from mild ones. If the patient is to be treated at home the other children, if there be any, should receive an immunizing dose of antitoxin and should be immediately sent out of the house. If this is not feasible they should be excluded from the sick-chamber and assigned to bed-rooms in the most distant part of the dwelling. Their hygienic condition should be looked after; at least they should be properly fed, regularly bathed and provided with plenty of fresh air day and night. Their throats and nostrils should be examined every day, and as soon as anything abnormal is discovered the child should be immediately separated from the others and given suitable treatment.

One of the uppermost rooms in the house should be selected for the patient. It should be light and properly heated, and provided with facilities for obtaining ventilation without incurring the risk from draughts An open fireplace, with at least a little fire burning, is a very desirable aid toward maintaining the purity of the air in the room. The most suitable temperature is 70° to 72° F. All unnecessary hangings, furniture and the like, that are liable to retain the contagium, should be removed from the chamber. In the winter months, when the heated air of the room is usually dry, it may be moistened by steam, which, if deemed advisable, may be slightly impregnated with eucalyptol, or some other fragrant essential oil. This is more especially advisable when the patient manifests croupy symptoms.

If more than one member of the family be ill with the disease care should be taken not to overcrowd the patients. Each patient should be allowed at least 2000 cubic feet of air space, with an additional allowance for the nurse. The nurse should be instructed to keep the patients as quiet as possible; at least, so far as active bodily movements are concerned. When the heart is found to be weak she should feed the patient by means of a feeding cup, and not allow him to rise or get out of bed under any circumstance whatever.

During the illness of the patient the privileges of the well members of the household should be restricted. They should be advised not to attend church nor public assemblages of any kind. The children, if

there be any, should at once be required to leave school, and should not be readmitted until the family physician or some qualified sanitary officer certifies that the sickness has ended, and that the house has been thoroughly cleansed and disinfected. The isolation of the patient should continue until the diphtheritic exudate has disappeared, and the affected mucous membrane has become entirely normal. When possible, cultures should be made to determine the absence of diphtheria bacilli; if two successively negative cultures be obtained it may be considered safe to allow the patient to associate with the other members of the family, provided he has had an antiseptic bath and is dressed in clean clothing.

As the bacilli may cling to articles which have been used by the patient, or which have been in the same apartment, all such articles as are worthless should at once be burned. Only such books, toys and the like, as may be burned at the termination of the illness should be allowed in the sick-chamber All articles for the laundry should be steeped for some time in a disinfecting solution, such as 4 fluidounces of strong carbolic acid to 1 gallon of water, and afterward boiled for one-half hour. For the disinfection of woolen goods formalin may be used, but for efficiency there is nothing that equals superheated steam. All utensils used by the patient in eating or drinking should be purified each time by means of boiling water. The secretions from the patient's mouth and nose should be disinfected by receiving them into a strong solution of chloride of lime, or a mercuric chloride solution (1 to 1000) or some other equally powerful germ-destroying agent. Small pieces of worn cotton goods, or cheesecloth, may be used to receive such secretions, and should be destroyed at once by fire.

The nurse or any other attendant should wear clothing made of such material as can be readily boiled and laundered. Before associating with well persons she should take an antiseptic bath, washing her hair at the same time, and change her entire clothing. The physician also should exercise care lest he himself may be the means of conveying the infection to others. He should not remain in the sick-chamber longer than is necessary to make a proper examination of the patient. Before leaving the house he should take the precaution to wash his face, hair and hands; the latter should be held for a few moments in some antiseptic solution, as mercuric chloride, 1 to 1000. He should delay visiting another patient until he has spent some time in the open air, or, what is better, changed his clothing. It is desirable for him to wear in the room a long rubber coat or linen gown, which should be kept hanging in the open air during the interval of his visits.

As the body of a patient who has died of diphtheria is still capable of transmitting the contagium, certain precautions in regard to it are necessary. An effort should be made to disinfect the body by thoroughly washing it with some powerful disinfecting solution. There is perhaps nothing more reliable than chloride of lime. Six ounces of this drug to 1 gallon of water makes a very effective germicide. The

body should be wrapped in a sheet saturated with this or some other similar solution before it is placed in the hermetically sealed casket, and the burial should follow as speedily as possible, without, of course, a public funeral.

When the illness has terminated, either by recovery or death of the patient, the sick-chamber and every article it contains should be thoroughly disinfected.

As already indicated, all washable goods in the room of the patient should be immersed in boiling water for one-half hour, and then laundered. Woolen clothing, mattresses, pillows, carpets and all other articles which cannot be laundered, should be so arranged in a room as to be thoroughly exposed to the influence of formaldehyde vapor. When feasible, such articles as those last named should preferably be sent to a disinfecting station and exposed to superheated steam under pressure for thirty minutes. All picture-books, toys and other things sent in for the amusement of the patient should be burned. After the room has been disinfected, cleansed and the paper on the wall changed, it should be thoroughly aired, and, if possible, remain unoccupied for a few days.

As some of these requirements would be only indifferently carried out by the average citizen, the local sanitary boards should have authority to exercise supervision over dwellings in which diphtheria makes its appearance, and should be provided with the necessary means and facilities for eradicating the infection. The work of disinfection should always be conducted by a properly qualified sanitary officer, and, as it is done in furtherance of public safety, the public treasury should supply the means. In every large city a suitable disinfecting station should be provided for purifying without cost all portable articles, particularly such as cannot be conveniently or properly disinfected at home. Philadelphia and many other cities of this country are provided with such facilities.

In order to afford health authorities the earliest opportunity to apply any or all of the measures which have been here indicated for restricting or preventing the spread of diphtheria, every case of the disease should be promptly reported as soon as the diagnosis is determined. In some municipalities the physician in attendance on a patient is required to give such notification—a requirement which, we think is not unreasonable.

Another means of preventing the dissemination of diphtheria, as well as other dangerous communicable diseases, is to apprise the public of the particular house in which it is present. How to do this without exciting opposition is a problem not easy of solution. The means adopted in many parts of this country is to affix, in a conspicuous place at the entrance of the house, a placard announcing the existence of diphtheria within. While this is usually distasteful to the householder, it serves the purpose of preventing any one from incurring danger unwittingly. But whether this plan be adopted or not, the

sanitary authorities should keep the premises under supervision, instituting visits from time to time by officers qualified and empowered to advise and direct the observance of proper sanitary precautions, and, if there be danger of non-compliance, to put in force more arbitrary restrictive measures.

Besides enforcing the preventive and restrictive measures which have been outlined, antitoxin should be administered as a prophylactic in households in which diphtheria has made its appearance.

LOCAL TREATMENT OF DIPHTHERIA.

With reference to the therapeutic indications in diphtheria, it is necessary to consider both the local and constitutional manifestations of the disease.

Faucial Diphtheria.—Severe local measures are objected to on the ground that they impair the continuity of the tissues, and thus facilitate the entrance into the system of the poisons generated by the Klebs-Loeffler bacilli and associated organisms. Impairment of the tissues also facilitates extension of the pseudo-membrane, for it is well known that the mucous membrane of the mouth, if not intact, is liable to become involved in the diphtheritic process. All caustic and irritating local applications are, therefore, to be condemned as being more harmful than beneficial.

After all, it must be admitted that gargles are of questionable utility. They can be used only in older children and adults; when most artfully used they do not reach much beyond the oral cavity. At the best they never touch anything beyond the anterior pillars, or not more than a small part of the tonsils. In severe cases gargles are objectionable, in that the patient is required to rise from the recumbent position when using them. They are to be recommended only at the beginning of diphtheria, or where the disease is of a mild character, and even then their use must be limited to patients old enough to perform the act of gargling.

We would not be understood as discouraging local applications in diphtheria; on the contrary, we believe that when used with good judgment they may be of great service. Any unirritating antiseptic solution may be employed, but after all, quite as much may be accomplished with a warm normal salt solution. It should be the aim of the physician to keep the parts involved as clean as possible without taxing too much the strength of the patient. Swabs should not be used, except by the physician or trained nurse, and then only with great care.

At the very beginning of diphtheria, or even when the disease is simply suspected, the throat should be sprayed every hour, at least for a few hours in succession, with a mild and unirritating antiseptic solution, such as a 1 per cent boric acid solution, diluted Dobell's solution, hydrogen peroxide with equal parts of water, or a solution of 1

to 4000 or 6000 of bichloride of mercury. Twenty-four hours will probably determine whether it is possible to prevent or limit the development of the exudation. If not successful, and the disease goes on to its fullest development, the same applications may be continued every hour or two for the purpose of cleansing the throat. As already mentioned, a warm normal salt solution will accomplish the same end. The irrigation of the throat is best carried out with the fountain syringe. So long as the fauces are covered with exudate hydrogen peroxide may be used without dilution, but when the exudate has thinned out very considerably, leaving the mucous membrane excoriated and irritable, it should be diluted with 1 or 2 or more parts of water. When the exudate has almost entirely disappeared, and the throat remains irritable, the following application is often useful:

℞—Menthol . . . . . gr. x
Oil of sweet almonds . . . . . f℥j—m
Sig.—Apply in form of spray.

Nasal Diphtheria.—As diphtheria of the nose and naso-pharynx is most dangerous, immediate and persistent local treatment should be adopted with the object of preventing, as far as possible, absorption of the noxious products. The treatment consists in frequent cleansing and disinfecting the nasal cavities. The remedies usually employed do not differ materially from those recommended in faucial diphtheria. The decomposing material and foul discharge should be washed away as fast as they form. In order to do this it is necessary to irrigate the nose very frequently—often every hour, or every two hours, day and night. In severe cases with a profuse fetid discharge the nares should be kept clean, no matter how much the child resists. The little patient may be restrained without suffering any harm by rolling him up in a sheet. If much exhausted, the child should not be raised from the recumbent position during the cleansing process. Only bland solutions should be employed, such as boric acid (5 to 10 gr. to the ounce of water), chloride of sodium (teaspoonful to 1 pint of water), or some other equally mild antiseptic solution. The nose wash should always be used lukewarm, and the more thorough the washing the better it is for the patient. Instillations with a small medicine dropper, so often used by physicians, are not sufficient. Nor will the atomizer convey a sufficient amount of liquid into the nasal cavities to accomplish the purpose aimed at. A small (not too small) blunt-pointed syringe will answer the purpose much better. If carefully used, there is perhaps no better irrigator than the fountain syringe. It should be held just high enough for the solution to flow without undue pressure, and thus obviate any possibility of injury to the middle-ear. If the nose inclines to bleed the irrigation should be very slow and gentle. But if the epistaxis be free and quite uncontrollable, as sometimes happens, the irrigation will have to be dispensed with. It may then become necessary to direct attention to the hemorrhage. Alum, tannic acid, Monsel's

solution and the like may be used. We have frequently found it necessary to plug the nares.

For the local treatment of nasal diphtheria many physicians prefer some of the more active antiseptic and disinfecting solutions, such as peroxide of hydrogen, permanganate of potassium, carbolic acid, bichloride of mercury and so forth. Peroxide of hydrogen is quite useful if it be properly diluted. It is very irritating to the mucous membrane of the nose, and will cause pain if not diluted with 8 or 10 parts of water. Carbolic acid has been used in solution varying from 1 to 1000 to 10 to 1000 parts of water. Care should be taken lest too much of this drug be swallowed. Permanganate of potassium has been highly recommended. It has been applied to the fetid nares with a cotton swab, in the strength of 1 to 250 of water, once or twice a day. For irrigation it may be used several times a day in a solution of 1 to 2000 to 1 to 4000.

For washing out the nares, as well as the fauces, bichloride of mercury in solution has many advocates. Its well-known power as a germ destroyer has led to its use. It would doubtless be more freely employed were it not for the danger incurred through its poisonous qualities. As young children always swallow some of the liquid that is injected into the nares, most physicians hesitate to use a solution which is so highly poisonous. The same objection holds good against its employment for irrigating the fauces. After some experience with most of the nasal washes mentioned above, we have, for the last few years, settled down to the use of warm normal salt solution almost exclusively. We find that it answers the purpose quite as well as any of the antiseptic washes, and that it has the advantage over some others of being perfectly safe and unirritating. We may add that we have used with benefit peroxide of hydrogen well diluted with lime water.

Aural Diphtheria.—But little treatment can be applied to the comparatively rare form of acute median otitis of diphtheritic character other than what is suitable for that affection when it occurs ordinarily. As pain is not often complained of, the condition is usually not realized until a purulent discharge issues from the external meatus. Nearly all that can be done then is to syringe the ear with a warm solution of boric acid or some other mild antiseptic wash. At the same time the nose may be irrigated with a similar solution. It is advisable that Politzer inflation be also employed with the hope of clearing the Eustachian tubes.

The insufflation of dry powders into the ear is not considered advisable, as they are likely to form dry crusts which may prevent the escape of the purulent material. Extension of the suppurative action to the mastoid cells rarely occurs; but when it does occur surgical treatment applicable to that condition should be resorted to.

Ocular Diphtheria.—For diphtheritic involvement of the conjunctiva, fortunately rare, the eye should be irrigated frequently—say

every hour—with a boric acid solution (10 gr. to the ounce of water) or some other equally mild antiseptic solution. This will be found difficult when the eyelids are very much swollen; but an effort must be made to keep the pus from accumulating under the lids. Ice applications, in the form of iced cloths, are always indicated at first; but later it may be better to use warm applications. A strong solution of nitrate of silver may be applied to the pseudo-membrane on the palpebral conjunctiva if care be taken to neutralize the silver salt immediately with a solution of chloride of sodium.

Paralysis of the muscles of the eye occurring as a sequel to diphtheria calls for no special treatment. It will almost always disappear entirely in the course of two or three months.

CONSTITUTIONAL TREATMENT OF DIPHTHERIA.

As diphtheria begins as a local disease very little internal treatment is required at the onset. Constitutional disturbance, however, occurs early, partly as a result of the local disease, but more especially from absorption of the toxic products of the diphtheria bacilli and the associated organisms. The prostrating effects of this poison are well known. The indications for internal remedies may be stated as follows: To aid the system in the elimination of the poison; to reinforce the debilitated vasomotor system; to improve the quality of the blood; to combat the poisonous effects of the toxins; to sustain the vital powers; and, lastly, to conduct to a favorable termination the secondary affections that may arise.

At the outset of the disease it is well to administer a gentle purge. For this purpose there is perhaps nothing preferable to calomel. Liquor ammonii acetatis (U. S. P.) is useful, as it tends to increase the secretions of the skin and kidneys. Water may be allowed *ad libitum*. Small pieces of ice held in the mouth will often have a soothing effect on the inflamed and painful fauces. Should the temperature of the patient be high, no attempt should be made to reduce it by the internal administration of antipyretic drugs, especially the coal-tar products, as they are too depressing. It is better to trust to tepid bathing. Bathing has the additional advantage of keeping the function of the skin active. At this early stage there is no article of diet equal to milk. There is, however, no objection to beef-tea and broth.

As soon as the diphtherial character of the disease is recognized *iron* may be administered. For the past seventy-five years this drug has had the confidence of physicians in this country, as well as those in most of the European countries, and by many it is regarded as our sheet-anchor in the constitutional treatment of diphtheria.

The preparation of iron that has achieved the greatest reputation in this disease is the tinctura ferri chloridi. It is believed to have both a local and general effect. It should be administered frequently and in positive doses. A child one year of age may take as much as 1 fluid-

dram in twenty-four hours, and a child three to five years of age from 2 to 3 fluidrams in the same period of time. It should be administered every hour or two. Some writers advise that it be given every fifteen, twenty or thirty minutes. It should always be given diluted with a little water, so that the dose is about a teaspoonful. The addition of glycerin makes the drug more palatable. One part of glycerin to 3 parts of water makes a very good vehicle. If there is too much dilution no local effect can be expected from the drug. As a rule, it is well borne by the stomach; but there are exceptional cases in which it is not tolerated at all.

We have used in our hospital work for many years the ferric chloride in doses practically the same as those last mentioned; but we prefer to combine it with the bichloride of mercury, as in the following formula:

℞—Hydrargyri chloridi corrosivi . . . . . gr. ¼
Tinct. ferri chloridi . . . . . ʒj
Syrup. simplicis . . . . . ʒj
Aquæ . . . . . q.s. ad fʒiij.—M.
Sig.—For a child three years of age 1 fluidram in a little water every two hours.

Strychnine is useful to combat cardiac depression. It may be given combined with tincture of the chloride of iron, or it may be administered separately. It is often advisable to inject it hypodermically. The dose should be adapted to the age of the child, but the amount which children of tender years will bear without harm is astonishing, especially when in a condition of toxemia. A child three years of age will take $\frac{1}{100}$ gr. every four to eight hours; in an emergency a larger dose will be borne.

Digitalis is also of advantage when the heart action is weak. In case of irritability of the stomach, which always occurs in profound toxemia, digitalin may be administered hypodermically. Strophanthus, sparteine, caffeine and the like are also recommended to combat cardiac failure. To a child five years of age 2 drops and sometimes as much as 4 drops of the tincture of digitalis may be given every four hours, or from 1 to 6 drops of the tincture of strophanthus. In a great emergency one or two unusually large doses of these drugs may be administered, followed by the more ordinary dose at proper intervals. Citrate of caffeine may be used in doses from ½ gr. to 5 gr.

There are but few other diseases which demand more imperatively the use of *alcohol* than does diphtheria. Mild cases will frequently do well without stimulants; but no case, however mild it may seem to be, should be considered out of danger until recovery has taken place. In view of the well-known depressing effects of the poison of this disease, even mild cases should receive small doses of some stimulant. Severe cases require a very liberal amount of alcohol in some form; it should be commenced early in the disease by giving small doses at first, and increasing the amount as the indications for its use become more pronounced. Whenever the heart action shows any loss of force,

or the first sound of the heart becomes less distinct, or pallor is noticed, or the patient's strength is declining, large and frequent doses of some active stimulant are required. It matters little how the stimulant is administered, whether plain or in the form of milk punch or wine whey, provided that sufficient is given to produce the desired effect.

Whiskey is more often employed, for the reason, doubtless, that good whiskey can be more easily obtained than good brandy. If whiskey disagrees with a patient brandy should be tried. Either of these stimulants may be administered in teaspoonful doses properly diluted to a child five years of age. In septic cases the amount of alcohol which a child may take without showing evidence of intoxication is nothing less than astonishing. In this type of diphtheria it is not unusual for a child five years of age to take 1 teaspoonful or even 2 teaspoonfuls of whiskey every hour, making the daily amount ingested from 3 to 6 ounces. While alcohol is ordinarily contraindicated in albuminuria or nephritis, yet rather than lose the support of so important an ally in combating toxemia, it should nevertheless be cautiously employed.

If the toxemia be well marked, alcohol in doses however large will not save the life of the patient, but it may prolong it somewhat. When the heart's action begins to wane, it is difficult to restore it. We cannot recollect of ever having seen a patient recover when the pulse was once lost at the wrist. Hence, the great importance of beginning the use of alcohol early. If the stomach will not tolerate either whiskey or brandy a good wine should be substituted. We have found champagne useful when the stomach is irritable. Aromatic spirit of ammonia is a good stimulant, and may be used temporarily, if it be found more agreeable to the stomach.

Attention should be given to the *diet* of a diphtheria patient throughout the entire illness. In the acute stage of the disease all food should be of a fluid character, consisting of milk, beef-tea, broths and the like. It may be necessary to peptonize these, though, as a rule, the digestion is not bad. Ice and iced drinks may be allowed. Should there be a craving after cold articles, cold junket, frozen custards and frozen beef-tea may be given. Soft-boiled eggs are useful when the patient is able to take them. Later, cornstarch, rice pudding, bread and butter, fruit and vegetables may be added. As early as possible a full, liberal diet should be allowed.

In regard to the complications of diphtheria, we feel that but little time need be spent here in discussing their treatment. Adenitis, otitis media, bronchopneumonia and nephritis are the more common complications encountered, and they present no indications for treatment at all different than when these affections occur from other causes.

The paralysis of diphtheria, however, differs from the other complications, in that it is peculiar to the disease. It cannot be prevented, and drugs avail but little in hastening the cure. The most dangerous form is cardiac paralysis. It is well to anticipate this condition by keeping the patient quiet and endeavoring to sustain the strength of

the heart by administering digitalis, strychnine, alcohol and other cardiac tonics. As we have already seen, cardiac paralysis often develops suddenly, and the patient may die before the physician can be summoned. The earliest symptoms of this affection should receive prompt attention. The patient should remain as quiet as possible in bed, with his head low. It is sometimes advisable to raise the foot of the bed slightly. He should remain in the recumbent position when taking food, water or medicine. Under no circumstances should he be allowed to leave the bed to empty his bladder or rectum. Whiskey or brandy should be given in doses sufficiently large to be of service. If the stomach be at all irritable champagne is to be preferred. In case of a sudden seizure of heart failure hypodermic injections of brandy should be administered. The hypodermic use of strychnine will also aid in sustaining the heart action. Ammonia, camphor, musk and the like sometimes serve as useful auxiliaries. At the same time the general strength of the patient should be well sustained with a liberal amount of nourishing and easily digestible food, such as peptonized milk, beef-tea, broths or some of the concentrated foods designed for invalids with feeble digestion. For large children and adults soft-boiled eggs are useful, unless the digestion be very feeble. When improvement takes place the physician should see that the patient does not get out of bed too soon.

For the multiple paralysis which follows diphtheria the patient requires sustaining remedies, such as iron, quinine, strychnine and alcoholic stimulants. Particular attention should be given to the diet, as there is ordinarily marked debility and anemia, with a feeble digestion. Beyond the employment of a sustaining treatment we do not believe that much can be done to hasten the cure of diphtheritic paralysis. Some physicians believe that they have derived benefit from electricity, but a large number speak doubtfully of its efficacy.

As strychnine is known to be efficacious in many other forms of paralysis, it is frequently employed on general principles for the neuroses of diphtheria. Some observers have reported good results from its use, while others question its utility, except as a tonic. Prof. Henoch, Reinart and Gerasimow claim to have hastened the cure of diphtheritic paralysis by hypodermic injections of strychnine. This drug is said to have been employed in one case (a boy, aged three and a half years), with marked improvement in the tonicity of the muscles within twenty-four hours after the first dose, which consisted of about $\frac{1}{60}$ gr., and this was repeated each day for fifteen days, when the patient was considered cured. In another case (a child, aged six years) a complete cure is reported from hypodermics of about $\frac{1}{75}$ gr. daily for seven days, followed by $\frac{1}{50}$ gr. each day for twelve days longer.

We are not convinced that strychnine possesses any special value as a remedy in diphtheritic paralysis. It is our opinion that tonics and a sustaining diet will do more toward helping a patient through an attack than anything else. The paralysis is seldom permanent.

We have never known it to be so. In most cases complete recovery takes place in from two to four months.

There is, however, one thing connected with the treatment of multiple paralysis of diphtheria which is of great importance. We refer to the care a patient should receive when unable to swallow. In all severe cases deglutition is difficult and sometimes impossible. It is necessary then to sustain the strength of the patient by nutritive enemata, or by introducing food into the stomach by means of an esophageal tube. The latter is preferable, as it gives us a better idea of the amount of nourishment that is utilized. The patient should be fed every four hours, and with each feeding there should be administered also such medicine, stimulants and the like as may be required. It is not often that a patient has to be fed with the esophageal tube for a longer time than two weeks. We recall one case of paralysis in which this means of feeding was employed for sixteen days. By holding the jaws slightly apart with the gag of the intubation set, it is not difficult to introduce the tube through the mouth into the stomach. The tube will slip down more easily if slightly oiled. If a patient be safely carried over the period of difficult or impossible deglutition, his chances of complete recovery may be considered very good.

SERUM TREATMENT OF DIPHTHERIA.

The discovery of diphtheria antitoxin and its use in the treatment of this infection constitutes one of the triumphs of modern medicine.

Thirty years ago diphtheria was one of the most dreaded of diseases, accompanied ordinarily by a mortality of at least 30 per cent, while the loss of life from the laryngeal form of the disease, particularly after tracheotomy, was simply appalling.

Shortly after Roux and Yersin (1888) had demonstrated that the symptoms of diphtheria were due largely to a soluble poison or toxin secreted by the bacilli Ferran, and later Frankel and Brieger (1890), undertook experiments in active immunization against diphtheria. About the same time von Behring discovered the antitoxin, and in a series of extensive researches with Wernicke he established experimentally its prophylactic and therapeutic value in diphtheria. The first attempt to apply this discovery to the cure of this infection of the human being was made in von Bergmann's Clinic (1891). The results, while encouraging, were not altogether satisfactory, owing largely to the fact that the serums were weak and the doses given too small. The discovery, however, resulted in creating an extraordinary stimulus to researches in immunity, and during the following two years more powerful serums were prepared, so that in 1896 a marked drop in the mortality of diphtheria was apparent in those places where the antitoxin was being used.

Since then diphtheria antitoxin has been the means of saving countless thousands of lives, and the treatment of diphtheria, instead of

being a reproach to medicine, has become the model of what the scientific treatment of an infectious disease ought to be. Statistics and the individual experience of those especially engaged in the treatment of diphtheria show that when the antitoxin is used on the first day of the disease, practically no mortality occurs. Parents and guardians should be taught this fact, and cautioned to seek medical advice promptly whenever a child complains of sore throat. While the use of diphtheria antitoxin is still decried and opposed by a few members of the medical profession—and this is not to be wondered at when it is remembered that cowpox vaccination still has its opponents—it is at least to be hoped that no physician will deprive a patient suffering from diphtheria of the benefits to be derived from the antitoxin treatment. *In the absence of special contraindications the refusal or neglect to use antitoxin in the treatment of diphtheria would, in the opinion of most physicians, constitute an act of criminal negligence and malpractice.*

Purposes of Serum Treatment of Diphtheria.—If we were always certain of seeing our patients on the first day of their illness, and if the disease could always be diagnosed in this stage, the treatment of diphtheria would resolve itself into an immediate dose of antitoxin and rest in bed two or three weeks. But patients frequently come under treatment comparatively late in the disease, or the true nature of the condition may not be fully diagnosed at first and treatment thus be delayed. Diphtheria is, therefore, still to be regarded as a dangerous infection, and while the proper use of antitoxin constitutes the most important part of the treatment, local applications, general constitutional measures, and the management of the various conditions that may complicate the disease are all to be considered. Here we will discuss only the serum treatment of the disease.

Bearing in mind the pathology of diphtheria, serum treatment aims to fulfil the following primary indications:

1. To neutralize all free toxin circulating in the body fluids, and also to neutralize, as much as possible, the toxin that has already united with the tissue cells.

2. To cause the destruction or removal of the bacilli producing the toxin as quickly as possible.

3. To furnish the patient with sufficient excess of antitoxin to neutralize the toxin as rapidly as it is produced until the virulent bacilli disappear.

Action of Diphtheria Antitoxin.—Diphtheria antitoxin best fulfils these requirements. In fact, there are no substitutes. In former days the powerful and irritant caustics and germicides that were freely applied to the throat, instead of limiting the disease and destroying the bacilli, probably actually encouraged its extension by excoriating and depressing the resistance of the surrounding mucous membranes.

1. The chief action of antitoxin is just what its name implies, namely, a substance that neutralizes the toxin. This is regarded as a chemical

reaction analogous to the neutralization of an acid by an alkali. When the antitoxin molecule has united with the toxin molecule it is believed that the toxin is neutralized and that both are rendered inert. As the result of experimental studies, however, we know that this union is not always a firm one, and it is possible for the toxin to become dissociated and attack body cells or other molecules of antitoxin, thus explaining in part the necessity for giving quite large doses of antitoxin—doses that are out of all proportion to what we would expect to be necessary, when considered weight for weight between guinea-pig and man, to effect complete neutralization of the toxin.

It is reasonable to presume, and may be accepted as true, that a stronger affinity exists between diphtheria toxin and antitoxin than between body cells and toxin. Just as the union between this toxin and its antitoxin is somewhat unstable, so, in like manner, it is probable that the union of toxin and body cells is not so firm but that it may, during an early stage, be dissociated to some extent by the more attractive antitoxin. This factor is to be borne in mind in the treatment of diphtheria, and is an additional argument for the administration of large doses of the serum.

2. Antitoxin pure and simple does not, however, constitute the only factor of value in antidiphtheric serum. While the pure antitoxin neutralizes the toxin, it has no injurious action on the bacilli themselves, and, indeed, it is said that the bacilli may live and multiply in the presence of large amounts of antitoxin. How, then, are we to explain the gradual disappearance of the membranous exudate and the bacilli at the local site of infection? It has been shown experimentally that virulent diphtheria bacilli resist phagocytosis. This condition is probably due to an actual leukotoxic action of the diphtheria toxin, aided by an aggressin-like action of the toxin which neutralizes opsonin, and in this manner prevents phagocytic activity. Kolmer,[1] in common with other observers, has shown that the antiserum as ordinarily produced neutralizes the antiphagocytic action of diphtheria bacilli, and enables the polymorphonuclear leukocytes to ingest them readily. Whether this is brought about through neutralization of the toxin by antitoxin, or is due to the presence of an immune opsonin (bacteriotropin) that lowers the resistance of the bacilli, or to the presence of an anti-aggressin that neutralizes the intrinsic defensive mechanism of the bacilli and thus favors phagocytosis, we are unable to state, but probably all three factors are operative.

3. As ordinarily prepared, diphtheria antitoxin possesses little or no bacteriolytic activity. Kolmer[2] has found, however, that antitoxin will fix complement with an antigen of diphtheria bacilli, indicating, therefore, the presence of bacteriolytic amboceptors. Serums produced by immunizing horses with unfiltered cultures of diphtheria bacilli instead of with the filtered toxin alone have been advocated for

[1] Jour. Med. Res., 1912, **26**, 373.
[2] Jour. Infect. Dis., 1912, **11**, 44.

the general and the local treatment, in the hope of securing lysis of the infected bacilli. Certainly it would appear wise to raise the bacteriotropic and bacteriolytic content of an immune serum by injecting the horses occasionally with unfiltered cultures, for it is highly probably that the action of the antiserum depends not only upon an antitoxin but also, to some extent at least, upon a bacteriotropin and possibly a bacteriolysin.

Subcutaneous Administration of Diphtheria Antitoxin.—Antitoxin is usually administered by *subcutaneous injection* into the tissues of the back, abdomen or buttocks. Experimental studies have tended to show that complete absorption does not occur until forty-eight hours after, although it is common clinical experience to observe improvement take place during the first twenty-four hours after injection.

Park[1] has shown that it takes twenty-four hours for the major part of the antitoxin to be absorbed by the blood from the subcutaneous tissues and some twelve hours from the muscles; two or three days are required for total absorption.

As will be emphasized later, *it is highly desirable and necessary to get antitoxin into the circulation as soon as possible after infection has occurred.* Usually this is best accomplished by giving antitoxin to every patient even suspected of being diphtheritic, and making the diagnosis afterward; the next best method is to administer the antitoxin in such manner as to favor quick absorption. *For this reason intramuscular and intravenous injection should be resorted to in all severe cases.* As previously pointed out, the Schick reaction in diphtheria has indicated that diphtheria toxin may be dissociated from tissue cells by large doses of antitoxin. Park and his associates have shown experimentally by this reaction that 20,000 units of antitoxin given subcutaneously were necessary to yield an effect equal to 1000 units given intravenously.

The subcutaneous route, therefore, should be used only in the treatment of mild infections. Intramuscular injections are just as easy, not more painful, and, as will be discussed in the succeeding paragraph, serum is absorbed at least three times more quickly.

Intramuscular Administration of Diphtheria Antitoxin.—Antitoxin does not become effective until it is absorbed in the blood and then passing through the capillary walls to the tissue fluids and cells. The greater the quantity in the blood, the more thorough and rapid will be the neutralization of toxin.

As previously stated, *intramuscular injections are given in the muscles of the thigh and buttocks, and since absorption is three to four times more rapid than by subcutaneous injection, there is no valid reason why intramuscular injections should not be used routinely instead of subcutaneous injections, particularly in the treatment of late cases and cases of more severe infections.* Rolleston and MacLeod,[2] Veeder[3] and numerous others have emphasized the value of intramuscular injections.

[1] Jour. Am. Med. Assn., 1912, **58**, 1976; Jour. Infect. Dis., 1914, **14**, 338.
[2] Brit. Jour. Dis. Child., 1913, **11**, 289. [3] Missouri State Med. Assn., 1915, **12**, 145.

Intravenous Administration of Antitoxin.—*Intravenous injections* are far more difficult, especially in children with fat arms and feeble circulations. An anesthetic or ten minutes struggling may do the patient harm, and unless the injection can be given with little disturbance and danger, the serum should be given by intramuscular injection. Not infrequently, however, an intravenous injection yields splendid results in severe and apparently hopeless cases, and in older children and adults this route of administration should be considered.

There can be no doubt, however, of the value of intravenous injections in severe cases and especially in late advanced cases. By these are meant cases already sick for twenty-four to seventy-two hours with rapid extension of the disease in the throat or nose, swelling of the tissues and glands and severe constitutional symptoms. According to Park,[1] antitoxin given intravenously passes out to the tissues about ten times as rapidly as when given subcutaneously and four times as rapidly as when given intramuscularly.

Intravenous injections are being given in increasing frequency; numerous reports advocating this route in the treatment of severe infections, whenever possible, have been made by many physicians. If it were not for the fact that the technique of administration is more difficult and the reactions sharper and more dangerous, the intravenous route would be the one of choice in the treatment of all but mild early cases.

In laryngeal diphtheria, however, the intravenous injection of antitoxin, while giving a quicker response, does not greatly lower the death-rate. In a series of 79 cases treated by Park and Mixsell with intravenous injections the mortality was 53.1 per cent. Bronchopneumonia developed in 45.5 per cent of the former series and in 51.9 per cent of the latter, and out of a total of 77 cases developing this dreaded complication only 5 survived.

Intravenous injections are apt to be followed in from fifteen to sixty minutes by a rise in temperature of 2° to 5° F. and a chill. The chill is not usually severe, lasts for five to forty-five minutes and occurs in about 40 per cent of cases. The temperature falls in a few hours to its former level or below and no bad effects are noticeable. These reactions are doubtless caused by the serum proteins producing a "protein shock reaction;" they are not dangerous, but are disturbing at the time and may impress the family unfavorably.

The syringe method is well adapted for the intravenous injection of antitoxin, as the bulk method of serum is usually small, especially if a concentrated antitoxin is being used.

Intraperitoneal Administration.—Toomey and his colleagues[2] have injected antitoxin intraperitoneally without dilution with saline solution, in the treatment of 50 cases of diphtheria and report the method as safe and simple, particularly in the treatment of severe cases with toxic myocarditis.

[1] Trans. Cong. Am. Phys. and Surg., 1916, **10**, 118.
[2] Am. Jour. Dis. Child., 1925, **29**, 214.

Oral Administration.—Antitoxin has also been given by *mouth* and even by *rectal injection*. The presence of a preservative, usually phenol, renders the oral administration objectionable.

McClintoch and King[1] have shown experimentally that antitoxin is absorbed after oral administration, but in an irregular and unreliable manner. If digestion is inhibited absorption is facilitated, and they have recommended that 1 minim of fluidextract of opium and 4 to 10 minims of saturated solution of salol in chloroform be added to each dose, and that no food be taken for at least four hours before administering the mixture.

While a therapeutic effect may be secured after large doses have been swallowed, there are very few occasions when this should be the method of choice.

Serum sickness does not usually follow oral administration, and the method may be of value in the treatment of diphtheria occurring in an individual extremely susceptible to horse serum. Furthermore, the method may be of value for continuing the effects of antitoxin when, by reason of fear on the part of the patient or for other reasons, injections cannot be given, although it is very doubtful if any good is accomplished, because absorption of antitoxin from the intestinal canal probably does not occur at all or but to a very slight degree.

Local Application of Antitoxin.—There does not appear to be any advantage in applying either fluid or dried serum antitoxin to the involved tissues in the nose or throat. The antitoxin itself is not directly bactericidal and the only good to be expected is that of cleansing, which may be done just as well with simple saline solution.

Importance of Early Treatment.—*The most important point to be observed in the treatment of diphtheria is to give antitoxin at once. It may be fatal to wait for the result of a culture, except perhaps in the case of the mildest of infections. In fact, the necessity for early administration of antitoxin cannot be overestimated. When once suspicion is aroused antitoxin should be given at once and the diagnosis may follow.* A few hours may make an enormous difference in the prognosis of any case, and while a dose of 2000 units of antitoxin may prove of the utmost value in checking diphtheria, it will do no harm whatever in case the disease is not present.

It is true that a physician will naturally hesitate to administer antitoxin unnecessarily; nevertheless, diphtheria is frequently a difficult disease to diagnose clinically, and is quite likely to be mistaken for tonsillitis. For this reason many physicians prefer to wait for the result of a culture, and this is proper, provided that the patient, especially in the case of a child, is given the benefit of the doubt by receiving 2000 units of antitoxin. *It is to be emphasized that a single negative culture does not exclude diphtheria.* As ordinarily made, about 80 per cent of primary cultures from genuine cases will show them to

[1] Jour. Infect. Dis., 1906, **3**, 701; 1909, **6**, 46.

be present in large numbers. A primary negative culture is most likely to be obtained from a patient having a heavy exudate, as the physician may rub lightly over the membrane, culturing the microörganisms of secondary infection and overlooking the diphtheria bacilli in the depths of the membrane adjacent to the diseased mucous membrane. To wait another twenty-four hours for a second culture still further reduces the patient's chances for recovery. *In the vast majority of instances, therefore, antitoxin should be given at once and repeated as often as is necessary until the correct diagnosis is established, and not one but at least two successive negative cultures should be obtained before diphtheria is to be excluded with any reasonable degree of safety.*

The following table, compiled from the annual reports of the Philadelphia Hospital for Contagious Diseases, shows the decided influence of early treatment upon the mortality of diphtheria. This table comprises cases of diphtheria alone, and does not include cases complicated by other diseases, such as scarlet fever and measles. *It is worthy of special notice that of 741 cases treated with antitoxin on the first day of the disease not 1 died.* Ker,[1] in an exceptionally rich exprience, has never seen a fatal result occur in a case that developed in a hospital and in which antitoxin was administered on the first day of the disease.

MORTALITY OF DIPHTHERIA ACCORDING TO THE DAY OF ADMISSION (WHICH ALSO INCLUDES THE TIME OF GIVING THE ANTITOXIN) IN THE PHILADELPHIA HOSPITAL FOR CONTAGIOUS DISEASES.

Year.	Total number of cases.	Mortality according to the day on which antitoxin was first injected.							Average mortality in diphtheria alone.
		First day.	Second day.	Third day.	Fourth day.	Fifth day.	Sixth day.	After sixth day.	
1904 . .	712	...	4.09	13.72	17.54	14.78	19.44	12.94	10.81
1905 . .	862	...	4.43	9.22	16.66	13.04	9.52	22.89	10.09
1906–1907	1239	...	3.45	12.90	10.85	13.08	29.41	6.09	8.70
1908 . .	1426	...	6.62	4.70	10.60	11.71	21.43	23.96	8.55
1909 . .	2153	...	4.61	7.13	10.72	9.35	7.25	13.33	6 60
1910 . .	1870	...	5.50	5.13	8.41	13.74	6.04	8.33	6.42
1911 . .	1895	...	6.91	9.41	7.12	11.04	7.22	2.66	6.86
1912 . .	1676	...	2.92	6.33	8.00	9.53	14.97	9.63	6.02
1913 . .	1273	3.92	6.51	6.52	6.87	4.76	12.50	18.80	7.63
Average .	13,106	0.4	5.0	8.3	10.7	11.2	14.2	13.1	7.96

Treatment of Paralysis.—It is generally believed that the paralyses of diphtheria are due to a toxone and not to the true toxin. Ehrlich believes toxone to represent a late secretory product of the diphtheria bacillus, whereas others regard it as a modified toxin. It is certainly apparent, however, that the bacilli should be gotten rid of as soon as

[1] Infectious Diseases, Oxford Medical Press, 1920.

possible, so as to eliminate the possibility of toxone production. This is best accomplished by the early use of large doses of antitoxin, aided possibly by judicious local treatment.

Zoeller[1] states that never has any tendency to paralysis been noted in healthy subjects or healthy animals treated with diphtheria antitoxin. The earlier in diphtheria the antitoxin is injected, the less the proportion of cases with paralysis. When the paralysis is once developed antitoxin should be given freely for three to five days. Comby has reported rapid cures under this in 13 cases. Massive doses should be given in early diphtheritic paralysis. With tardy paralysis it should also be given if not administered before, and also when the patient is a carrier. If it does no good, at least it does no harm. Sometimes small doses answer the purpose. Ginestious witnessed subsidence of a paralysis of accommodation, which had persisted for two years, when two injections of 10 cc. of antitoxin were given.

Dosage of Diphtheria Antitoxin.—While it is now generally agreed that the doses of from 100 to 200 units, such as were commonly given during the early years of antitoxin therapy, were far too small, there is still some difference of opinion regarding the proper doses to employ. Since the severity of the disease varies so markedly, no hard-and-fast rules can be given. The physician who has a clear idea of the nature of diphtheria and of the action of antitoxin, and knows what to expect of the latter in the treatment of the disease, should have no difficulty in properly treating a case of the disease.

In administering antitoxin the physician must be guided by the clinical condition of the patient, as we have as yet no practical laboratory method for estimating the degree of the toxemia. Treatment may be regarded as satisfactory when:

1. The local patch of exudate has ceased to spread and shows indications of disappearing.

2. The general condition of the patient is improved, *i. e.*, the toxinemia is decreased, the pulse grows stronger and more regular, and the patient feels more comfortable.

The temperature is not a reliable guide, for not infrequently in severe infections it may be normal or subnormal throughout.

So long as the exudate shows no signs of loosening and disappearing, but tends to spread, and so long as the general condition remains unimproved or grows worse, large amounts of antitoxin should be given. No case should be regarded as hopeless until death supervenes.

Every case of diphtheria is to be treated individually, rather than by any set rule. The amount of antitoxin given in the *initial dose*, and in subsequent doses as well, is dependent on the following factors:

1. The situation and extent of the lesion.
2. The general condition of the patient.
3. The day of the disease.
4. The age of the patient.

[1] Rev. d. méd., Paris, 1923, **40**, 157.

1. **The Situation and Extent of the Lesion.**—In ordinary *tonsillar diphtheria* in which there is a small patch on one tonsil, and which is first seen on the second day of the disease, the initial dose should be at least 5000 units. When the exudate involves the pillars of the fauces, the uvula, the posterior pharyngeal wall, or is well forward on the palate, this dose should be doubled and 10,000 units be given.

Cases that present laryngeal symptoms in addition to faucial lesions should never receive less than 12,000 units. In well-marked laryngeal diphtheria with dyspnea and partial suffocation at least 20,000 units should be given, preferably by intramuscular or intravenous injection.

Bronchopneumonia is the most dreaded complication of laryngeal diphtheria and is responsible for the majority of deaths. Out of a series of 77 cases studied by Park and Mixsell only 5 recovered, making a death-rate of 93.5 per cent. Of 81 cases laryngeal diphtheria not developing bronchopneumonia the mortality was 7.4 per cent.

Hogan[1] has stated that 82.11 per cent of the deaths from diphtheria in Baltimore have been due to laryngeal infections, and makes a special plea for earlier diagnosis, earlier administration of antitoxin and intubation.

In *nasal diphtheria* a distinction must be made between those cases that exhibit merely a dirty, chronic discharge containing bacilli, in which 2000 units may suffice, and those that present an actual membrane accompanied by well-marked toxic symptoms, when a large amount of serum—at least 10,000 units—should be given. Owing to the ready absorption of toxin by the nasal mucosa, a small patch in the nose may be accompanied by severe general toxinemia and frequently requires energetic treatment.

In diphtheria of the eye, vulva or of wounds relatively large doses should be given—at least from 10,000 to 20,000 units.

All of these doses must be regarded merely as suggestions for the initial dose in cases seen on about the second day of the disease. Physicians with extensive hospital experience, for example, Woody and McCullom, generally favor large doses, and while in private practice the question of expense and economy may be a factor, the physician will be wise to err on the side of safety and give a little too much serum rather than too little, especially in the first dose, when so much depends upon how soon antitoxin is introduced into the body fluids.

2. **The General Condition of the Patient.**—The general condition of the patient, or the effect which the toxinemia will have on the patient, is highly important in estimating the dosage of antitoxin. A patient who is pale, drowsy, prostrated and has a weak and irregular pulse, who has large masses of glands around the neck, or who has marked albuminuria, will require a much larger dose than one who presents none of these signs. Two persons of about the same age and suffering from the same lesions may show very different degrees of toxinemia.

[1] Jour. Am. Med. Assn., 1921, **77**, 662.

In the severe cases we must administer the maximum dose and repeat it at suitable intervals until an effect is produced.

3. **The Day of Illness.**—The day of illness on which the patient comes under observation is important in deciding the initial dose of antitoxin. For corresponding tonsillar lesions a dose of 2000 units on the first day may do more good than 5000 units given on the fourth day. Ker gives second-day cases of purely tonsillar diphtheria 3000 units, and adds an additional 1000 on the following day.

4. **Age.**—If the age of the patient exerts any influence at all on dosage, it indicates that more antitoxin should be given to children than to adults with corresponding lesions, as the disease is more fatal in children. So far as infants are concerned, Ker seldom gives more than 4000 units at a single dose, which should be an adequate amount when we consider the small size of the patient. Children over one year of age should be given from 5000 to 10,000 or more.

Repeating the Dose.—Whether or not subsequent doses of antitoxin will be required is dependent upon the circumstances of the individual case. In ordinary cases if on the day after treatment is commenced there is no diminution in the amount of membrane visible and the general symptoms have not improved, the dose should be repeated. If the membrane has spread and the toxinemia is worse, the second dose should be larger than the first. In septic cases the second dose may be given in from six to ten hours after the first. If the symptoms are less urgent the interval may be extended to twelve, but should never exceed twenty-four, hours.

One thing is certain—a part of what should be the first dose should not be held back to be given later. When the first dose has been of sufficient size the second and third injections are not required. As previously stated, subsequent injections may result in the neutralization of toxin already united with body cells, but most depends upon a large single dose as early in the disease as possible.

The Importance of Large Doses of Antitoxin.—As to the *total amount of serum to be administered*, continued injections at relatively short intervals are required until improvement has taken place. As long as a membrane is present and the patient is toxic it is probably worth while to push the treatment unless these show a tendency to clear away. Time must be allowed for absorption to take place, and the serum should not be pushed so far as to be wasted, and, quite possibly, excreted unchanged. The remedy is expensive, especially in private practice, and it is obviously desirable to have due regard for economy. While, as previously mentioned, physicians of such wide experience as McCullom, of Boston, and Woody, of Philadelphia, frequently give 200,000 or more units in severe cases of diphtheria, others, *e. g.*, Ker, of Edinburgh, have never given more than 64,000 units to a single patient, and, indeed, several of our colleagues of wide experience claim that they have secured excellent results in severe infections with doses that seldom exceeded 10,000 units.

The following table by Park summarizes well these questions of dosage and route of administration:

DOSAGE OF UNITS OF ANTITOXIN IN DIPHTHERIA—SINGLE DOSE ONLY.

Mild cases. (Subcutaneous or intramuscular injection.)	Moderate cases. (Intramuscular or subcutaneous injection.)	Severe cases. (Intramuscular or one-half intravenous and one-half intramuscular or subcutaneous.)	Malignant cases. (One-half intravenous one-half intramuscular.)
For Infants, 10 to 30 Pounds (Under Two Years of Age).			
2000 to 3000	3000 to 5,000	5,000 to 10,000	10,000
For Children, 30 to 90 Pounds (Under Fifteen Years of Age).			
3000 to 4000	4000 to 10,000	10,000 to 15,000	10,000 to 20,000
For Adults, 90 Pounds and Over.			
3000 to 5000	5000 to 15,000	10,000 to 20,000	15,000 to 40,000

Treatment of Relapses.—Occasionally after a patient has recovered from an attack of diphtheria the infection recurs after several weeks. It is in such cases that the physician hesitates to administer antitoxin on account of the discomforts occasioned by serum sickness. It is true that serum sickness is more likely to follow in these than in primary cases, and the very profuse and itchy eruption, joint pains and fever do indeed render the patient quite uncomfortable. Since a relapse is usually, although not always comparatively mild, the serum may be dispensed with if there is no involvement of the larynx and if there is not much evidence of toxinemia; otherwise full doses of antitoxin should be given without hesitation. The subcutaneous injection of 0.5 cc. of the serum two or three hours before the main dose is given may possibly produce a condition of anti-anaphylaxis and ward off the more dangerous symptoms. If respiratory difficulties should follow a reinjection of serum, adrenalin chloride, atropine and caffeine should be administered hypodermically.

Value of Diphtheria Antitoxin.—At the present day it seems hardly necessary to introduce elaborate statistics to prove the value of antitoxin in the prophylaxis and treatment of diphtheria.

1. It is generally admitted that most of the reduction in the mortality of diphtheria cannot be attributed solely to the use of antitoxin, for unquestionably bacteriologically diagnosis has permitted the inclusion, in our statistics, of a certain number of cases that, twenty years ago, would not have been classed as diphtheria. Generally speaking, however, the mortality of diphtheria, considering all types of infection coming under observation at varying intervals after the disease has developed, *is at least five times less under antitoxin treatment than when it is treated without antitoxin.* This proportion is true, whether we compare the general mortality before 1896 with the present rate, or whether we take a large city and compare the mortality under both forms of treatment for a single or for several years. For example, in

Philadelphia the mortality-rates per 100,000 of population for the five years preceding the use of antitoxin were as follows:

1891	127.4
1892	156.3
1893	103.9
1894	122.5
1895	115.9

In five years following the general use of antitoxin the mortality-rates per 100,000 population were as follows:

1906	37.78
1907	34.60
1908	33.35
1909	33.60
1910	31.70

In Philadelphia, during the years 1909–1910 and 1911, the average mortality of diphtheria treated with antitoxin in the Philadelphia Hospital for Contagious Diseases was 9.9 per cent, and in the private practice of physicians, 13.07 per cent. In contrast to these figures is the mortality of 40.34 per cent in the private practice of those physicians (fortunately few) who refused to give antitoxin or in those families opposed to its use.

Kossel[1] has stated that in Germany prior to the use of antitoxin (1886 to 1894) the mortality from diphtheria was from 85 to 130 per 100,000 inhabitants; since 1899 it has never reached 30.

The average mortality in 13,106 cases of pure diphtheria treated with antitoxin in the Philadelphia Hospital for Contagious Diseases during the years 1904–1914 was only 7.96 per cent. As stated elsewhere, when this is compared with the average mortality of about 41 per cent when no antitoxin was used, it is not difficult to appreciate the therapeutic value of the remedy.

2. As previously stated, it is also worthy of note that there is practically no mortality in diphtheria cases receiving antitoxin on the first day of illness. *During nine consecutive years (1904–1913), covering the treatment of 741 such cases in the Philadelphia Hospital for Contagious Diseases, not a single death occurred.* During 1913, 2 of the 51 first-day cases died.

It will also be noted that the patient's chance for recovery grows steadily less with each day that the administration of serum is delayed, and this should be evidence enough to convince any right-minded person that we possess in antitoxin a remarkable remedy for the treatment of diphtheria.

3. The influence of antitoxin is also noted in the mortality of laryngeal diphtheria. While the mortality in this condition is still high, owing to the frequency and dangers of bronchopneumonia and the necessity for operative measures, it has been reduced at least one-

[1] Deutsch. med. Wchnschr., 1915, 41, 1445.

half since antitoxin came into general use. Prior to 1896 the mortality was at least 70 per cent; since then it has been reduced to 35 per cent or less. As shown in the following table, of 1207 cases treated in the Philadelphia Hospital for Contagious Diseases, the average mortality was 35.6 per cent.

MORTALITY OF LARYNGEAL DIPHTHERIA (INTUBATION CASES) IN THE PHILADELPHIA HOSPITAL FOR CONTAGIOUS DISEASES.

Year.	Total number of cases.	Mortality according to day upon which intubation was performed.							Average mortality.
		First day.	Second day.	Third day.	Fourth day.	Fifth day.	Sixth day.	After sixth day.	
1903	67	66.6	25.30	21.80	30.90	22.50	...	45.00	26.60
1904	125	...	39.20	29.03	73.68	33.33	70.00	36.84	39.20
1905	136	...	30.76	39.39	50.00	21.42	16.66	42.30	36.76
1906–1907	72	...	50.00	55.00	40.74	45.45	71.92	28.57	49.29
1908	162	...	29.26	50.00	33.33	30.76	9.09	38.88	33.95
1909	183	...	50.00	44.18	38.88	23.81	53.84	40.00	42.62
1910	89	100.0	55.00	33.33	28.58	50.00	...	36.46	39.34
1911	104	50.0	76.66	55.55	52.63	36.36	...	27.27	54.80
1912	133	30.0	58.33	41.93	48.27	50.00	63.67	50.00	48.87
1913	136	100.0	65.91	63.64	35.29	25.00	47.82	68.00	58.82
Average	1207	...	...	...	...	...	...	...	35.6

Formerly when a child contracted diphtheria the parents were warned of the likelihood and danger of the infection involving the larynx and trachea; nowadays this possibility is quite remote.

4. Finally the claim of the opponents of the serum therapy of diphtheria that antitoxin increases the percentage of paralyses is without foundation. While it is true that this percentage is somewhat higher than was noted in former years, this increase is to be explained by the fact that antitoxin saves a larger number of severe cases long enough for them to manifest paralyses, and, second, by the greater attention that has recently been directed to its milder forms. Since diphtheritic paralysis is regarded as caused by toxone or a later secondary toxic product of the bacilli, the indications are to rid the patient of the bacilli as quickly as possible, and this is best and most surely accomplished by the proper administration of antitoxin.

Normal Horse Serum and Other Non-specific Agents in the Treatment of Diphtheria.—Binge[1] has treated 466 cases of diphtheria with subcutaneous injections of normal horse serum, and the results based upon mortality, duration of disease and number of complications showed no marked differences from 471 cases treated with immune horse serum (antitoxin). Others have employed normal horse serum with similar results, the subject having been recently reviewed by

[1] Deutsch. Arch. f. klin. Med., 1918, **125**, 284.

Klotz[1] and doubtless a part of the beneficial results of the antitoxin treatment of diphtheria are to be ascribed to non-specific effects produced by the serum proteins. This may be one reason why not a few of the older physicians believe that the old-fashioned raw serum antitoxin gave better results than the solutions of concentrated globulins now in common use, although the incidence of serum disease was higher. Calhoun,[2] Kraus and Sordell[3] found that normal horse serum had little or no effect upon neutralizing diphtheria toxin injected into guinea-pigs, but this does not exclude the possible beneficial non-specific effects in human beings from injections of normal or antitoxic horse serum.

Lüdke has treated 15 cases with 2 to 3 subcutaneous injections of 3 to 5 cc. of 10 per cent solution of albumoses, and claims that the results compared favorably with those observed with antitoxin therapy.

TREATMENT OF LARYNGEAL DIPHTHERIA (MEMBRANOUS CROUP).

It is deemed most convenient to consider the treatment of laryngeal diphtheria under three heads:

1. Prevention.
2. The means of promoting the separation and expulsion of the pseudo-membrane.
3. The adoption of such operative measures as will overcome the mechanical obstruction to respiration.

Prevention.—There is no certain way of preventing laryngeal diphtheria, unless it be to guard the child against exposure to the infection of the disease. But when diphtheria begins in the fauces something may be done in the way of diminishing the liability of the membrane extending into the larynx. We have seen that a mucous membrane which is inflamed or congested is thereby predisposed to the diphtheritic process. It is advisable, therefore, to guard the patient, as far as possible, against the development of a catarrhal affection of the larynx. As soon as faucial diphtheria is recognized the physician should see that the child is placed in a room of equable temperature and free from draughts. If the case occurs in the winter season, and the atmosphere of the room is warmed by dry heat, it would be well to moisten the air by the addition of a little steam. It has been suggested that the steam be impregnated with eucalyptol or some other fragrant essential oil, but we do not think that this is of any great importance. Care should be taken not to overcharge the air of the room with moisture, as this would be more harmful than beneficial. In the summer months fresh air should be freely admitted, with precautions against draughts, and steam may be dispensed with.

[1] Berl. klin. Wchnschr., 1919, **46**, 987.
[2] Am. Jour. Dis. Child., 1921, **21**, 107.
[3] Ztschr. f. Immunitätsf., 1921, **31**, 107.

Drugs are of no avail in preventing laryngeal involvement. Antitoxin may be of great service as a preventive measure, but we have seen the pseudo-membrane in the fauces extend into the larynx on a number of occasions even after the administration of antitoxin.

Means of Promoting Separation and Expulsion of the Pseudo-membrane.—When false membrane has formed in the larynx, constituting membranous croup, Nature's method of effecting a cure consists in the gradual disintegration of the membrane, or its separation and expulsion. How this process may be best promoted has always been a problem difficult of solution. *Emetics* have been freely employed, and of these turpeth mineral was for a long time believed to be especially useful. But they can be of no service unless the membrane be in good part detached. The persistent use of emetics is objectionable on account of their depressing effect. When, however, a flapping sound is heard in the larynx, indicating the presence of partly detached membrane, an emetic should not be withheld except in cases of profound asthenia. The one selected should be of that class which excites prompt and efficient vomiting without producing prolonged nausea and depression. Among those to be preferred we would mention ipecacuanha, powdered alum and sulphate of zinc.

For the purpose of hastening the separation of the false membrane in croup there is a general consensus of opinion in favor of the continuous inhalation of warm steam. This is frequently impregnated with an alkali, like lime, or with some mild antiseptic agent, like eucalyptol, the compound tincture of benzoin, or turpentine. But it is the steam upon which the chief reliance is placed. Oertel believes that the energetic use of hot vapor causes a rapid and abundant suppuration of the diseased tissue, until finally the pseudo-membranous layer becomes completely detached from the rapidly regenerating tissue of the mucous membrane, and is expelled either piecemeal or in its entirety. He regards this as Nature's process of resolution in favorable cases.

The inhalation of warm steam is undoubtedly at times of much benefit, but we are inclined to believe that this treatment is often carried to excess. When shut up in a tightly closed tent in which a basin of water is kept constantly boiling, the child receives not only a diminished supply of oxygen, when the blood is already suffering from an oxygen dearth, but his skin is kept bathed in moisture, and his clothing and bedding are constantly damp. The effect of such treatment is certainly depressing. Warm steam inhalation should therefore be employed with some care.

Suction.—Litchfield and Hardman[1] have described a method of treatment employing a suction apparatus similar to that used in tonsil operations for removal of blood and mucus. In the Philadelphia Hospital for Contagious Disease it has been in use since 1924, and Dr.

[1] Jour. Am. Med. Assn., 1923, **80**, 524.

Woody, the medical director, states that the results have been highly gratifying, in that it has enabled him to cure without operation a great many cases which otherwise would have required the operation of intubation. When we remember that a patient when intubated has but 7 chances out of 10 for a recovery, and when we further remember that all cases that respond favorably to this new treatment are able to avoid intubation, we readily understand that this innovation has resulted in the actual saving of human life. More than this, the patients who respond favorably are discharged as cured after a short stay in the hospital, most of them after as short a residence as two weeks. Such cases when intubated are often detained in the hospital for periods of time varying from two weeks to several years. It can thus be seen quite easily that laryngoscopy and aspiration not only save human life, but by shortening the patient's stay in the hospital bring about less physical suffering to the patient, and mental anxiety to the parents, besides a great saving of labor and money to the hospital.

Antitoxin Treatment.—As previously stated, large doses of antitoxin are required, and the dose should not be less than 10,000 units even in infants. In well-marked cases 20,000 units or more are generally required, preferably by intramuscular or intravenous injection, and repeated in six to twelve hours.

Avoiding Tracheotomy and Intubation.—The frequent deaths after tracheotomy and intubations compelled Schlossmann[1] to try to avoid them as much as possible. In his opinion man requires much less air than we think, especially when resting. Therefore the main effort should be directed to procure with narcotics a rest for the child during the twelve or more hours before the antitoxin begins to work. The window should be open, and the cooler the air, the better for the child, who should be well covered and warmed with bottles. The prognosis of his patients improved with the avoiding of tracheotomy or intubation except in the gravest cases. Burghard[2] also states that narcotics and an open window are of value, although if stenosis progresses during the first twenty-four hours after the injection of antitoxin, tracheotomy is resorted to. Connerth[3] reports that in 81 cases tracheotomy was superior to either intubation or expectant treatment in children under two years of age.

Operative Measures.—If it be found that the laryngeal symptoms do not improve under the treatment recommended, but, on the contrary, become more and more marked, or if the patient be not seen until the symptoms of mechanical obstruction have become alarming, recourse must be had at once to operative measures. The operation which is necessary to overcome the difficulty is either tracheotomy or intubation. Formerly tracheotomy was universally employed, but of late years it has been almost entirely superseded, in this country particularly, by intubation.

[1] Deutsch. med. Wchnschr., 1924, **50**, 941. [2] Monatschr. f. Kinderh., 1926, **31**, 626.
[3] Deutsch. med. Wchnschr., 1925, **51**, 188.

Intubation.—This procedure is viewed more favorably, mainly because it does not require the use of the surgeon's knife. We all know how reluctantly parents give their consent to the operation of tracheotomy on their child. When this operation was the only means of overcoming the obstruction to the entrance of air through the larynx, it was too often postponed until the child was almost moribund, and, consequently, the results were discouraging. Intubation being a bloodless operation, and not requiring an anesthetic, parents do not hesitate to give their consent to this procedure, and hence the lives of many children who suffer from membranous croup are now saved that would otherwise be lost. It is a matter of great importance that operative interference, whether intubation or tracheotomy, be not delayed too long. It is almost criminal to allow a child to die from suffocation without making an effort to save its life by resorting to one or the other of these mechanical measures. While intubation is to be preferred in most cases, it cannot always take the place of *tracheotomy*. A physician without experience in intubation would be likely to fail in the operation, and if no one possessing the necessary skill is available he would be obliged to resort to tracheotomy. Or the latter operation may be preferred, or even become necessary, when the membrane extends far down into the trachea. In such cases the intubation tube will not afford relief. *Tracheotomy* may also become necessary when the intubation tube is repeatedly coughed up.

The procedure for relieving the stenosis of membranous croup by placing a tube in the larynx with its upper end below the epiglottis was first adopted by Bouchut in 1858. But, as his devices were crude, and as the operation was deemed impracticable by his confrères, and even ridiculed by them, he was discouraged from pursuing farther his conception of intubation. It remained for Dr. Joseph O'Dwyer, of New York, to devise and perfect the instruments necessary for the operation and to demonstrate beyond question the utility of the procedure.

O'Dwyer's work of devising the intubation tubes was begun in 1880, without, it is said, any knowledge of the previous experiments of Bouchut. It required, however, some four or five years of diligent experimentation before the set of intubation instruments was evolved into its present state of perfection. The New York Academy of Medicine has in its possession a complete collection of all the instruments used by O'Dwyer in his long series of experiments. The collection is interesting as showing the various changes in the size, shape and constructon of the intubation tube in its evolutionary process.

The Indications for Operative Interference.—When operative interference is required intubation, as already mentioned, is the operation to be preferred. But whether it be intubation or tracheotomy, the indications for operation are the same. If, in spite of the treatment which has been recommended for membranous croup, there is progressive asphyxia, as evidenced by increasing dyspnea, labored breathing,

stridor, suppression of voice, cyanosis, retrocession of the supraclavicular fossæ, as well as of the epigastrium and the lower ribs, the operative procedure should not be delayed.

Intubation is not so simple an operation as to be resorted to indiscriminately. When introduced, the tube acts, of course, as a foreign body in the larynx and is not incapable of doing harm, to say nothing of the slight abrasion that may result from its introduction, even by skilled hands, its presence in the larynx for several days is liable to cause ulceration at the points where it impinges. But, notwithstanding this fact, when the indications for intubation are clear and unmistakable it should be performed at once. Do not wait until the pulse begins

FIG. 136.—The first steps of intubation in the upright position.

to flag and the child's strength becomes exhausted, else death may suddenly occur from heart-failure. We repeat that when there is a marked retrocession of the epigastrium at each inspiratory act, and cyanosis is evident, intubation should not be delayed another moment. By waiting longer nothing but harm can come to the lungs and to the heart.

The Technique of Intubation.—No anesthetic is required for this operation, but it is necessary that the child should be brought under perfect control. This may be accomplished by placing the child's arms downward in a straight line with the body and rolling him up in a sheet or light blanket. In thus preparing the child care should be taken to avoid having too great a bulk of the blanket on the chest

FIG. 137.—Intubation; pulling forward the epiglottis.

FIG. 138.—Intubation; introducing the tube into the larynx.

of the child, as this will interfere with the manipulations of the operator. The child should then be placed on the lap of a nurse seated in a chair, with its head somewhat above her left shoulder. She should grasp the child in her arms, and hold its legs firmly between her knees. (See Fig. 136.) The child is thus brought under complete control, with no great increase to its discomfort.

The gag should now be placed between the jaws of the child on the left side, and held by the assisting physician or nurse, who, standing behind the child, steadies also its head with a firm grasp of his hands. It is assumed, of course, that the operator has already selected the tube suited to the age of the child, that he has inserted into the eyelet of the tube a silk ligature or string, which, when both ends are tied together, is long enough to reach nearly to the end of the handle of the introducer, and that he has affixed the obturator with its tube to the introducer. It is advisable to see that his instruments work well by pushing the tube off of the obturator once or twice before beginning the operation.

All preliminary arrangements being completed, the operator, sitting or standing, as he may prefer, in front of the patient, inserts his left index finger and feels for the epiglottis. Having secured it, he pulls it forward on the base of the tongue, keeping his finger as much to the left as possible. With the introducer in his other hand, he passes the tube over the dorsum of the tongue until it reaches the chink of the glottis, when the handle of the introducer should be quickly raised so that the tube may pass downward into the larynx. It should then be pushed off and the obturator withdrawn, the tip of the finger meanwhile, being held on the head of the tube to prevent its being pulled out. The operator should not let go the string until he is sure the tube is in the larynx. Its presence in the larynx is known by the shrill, metallic cough and by the relief of the dyspnea. If the tube has been introduced into the esophagus there is, of course, no relief. This location of the tube may also be recognized by the fact that the string grows shorter as the tube descends into the esophagus. It should be pulled out at once.

The tube being properly placed, it is well to remove the mouth gag and allow the child to cough and expectorate for a minute or two, and at the same time to be sure that there is no obstruction in the tube. Everything being satisfactory, the gag should be reintroduced, the string cut and withdrawn, while the tip of the index finger rests on the head of the tube to prevent its displacement. The child should then be released and put to bed.

If the child is very young, having no molar teeth, and the operator distrusts his ability to remove the tube with the extractor, the string, instead of being cut and withdrawn, may be looped over the ear of the child and secured to the cheek with a strip of adhesive plaster. In this case the hands of the child must be muffled, else the offending string will be caught with the fingers and the tube pulled out. In children with teeth this procedure is not to be recommended, as the

string is soon chewed off and rendered useless. Experienced operators, however, prefer to remove the string in all cases.

There are still some other points in connection with the operation that the beginner should know. In the first step of the operation the operator's hand containing the introducer should be close to the chest of the patient. The tube should be pushed backward on the median line of the tongue until it reaches the chink of the glottis, then the handle of the instrument must be raised, and the tube should slip down into the larynx without much force being used. The tube during its introduction sometimes causes a slight spasm of the parts, in which case the operator should pause for a few moments, when the spasm will probably relax and the tube slip into place. It should be remembered that the epiglottis must be kept out of the way; if not the operation will surely fail. It is important, too, that the child should be under perfect control in the arms of the nurse, and that it should squarely face the operator. The position of the child's head and neck should be, as Northrup says, as if the child were suspended from the top of its head.

In case the first attempt at placing the tube is unsuccessful, rather than exhaust the patient with repeated trials at one sitting it is better to remove the gag and allow the child a few seconds to rest, or to cough and expectorate. A beginner rarely succeeds the first time; it is far better that he should make several short attempts than a prolonged one.

A vigorous cough following the introduction of the tube is favorable rather than otherwise, as it shows that the parts have not lost their sensitiveness, and it clears the mucus from the trachea. If there is no cough, and the breathing ceases and the cyanosis deepens, there is surely an obstruction at the lower end of the tube; in which case it should be removed immediately. If the same result follows a repetition of the operation tracheotomy should be performed.

Some operators prefer to have the child in the recumbent position during the act of intubation. The advantages claimed for this position are that the operation can be performed with but a single assistant and that there is less danger of heart failure if the patient be greatly prostrated. The child should be rolled up in a sheet or thin blanket, as already described, and placed squarely on its back. In other respect the operator should proceed as before. At the present time the resident physician in the Philadelphia Hospital for Contagious Diseases employs this method altogether.

Dangers and Difficulties of Intubation.—The operation cannot be said to be dangerous when performed by an experinced operator. It is true, instances have occurred in which exudate has been pushed down into the trachea by the tube, causing suffocation and instant death. This condition, however, is easily recognized at once, and the prompt removal of the tube is usually followed by forcible expulsion of the detached mass of false membrane. When this occurs the dysp-

nea may be so greatly relieved that reintubation is not necessary. But frequently the membrane reforms and the operation is again called for.

Under the circumstances just mentioned, we would emphasize the importance of removing the tube promptly; for if there is too much

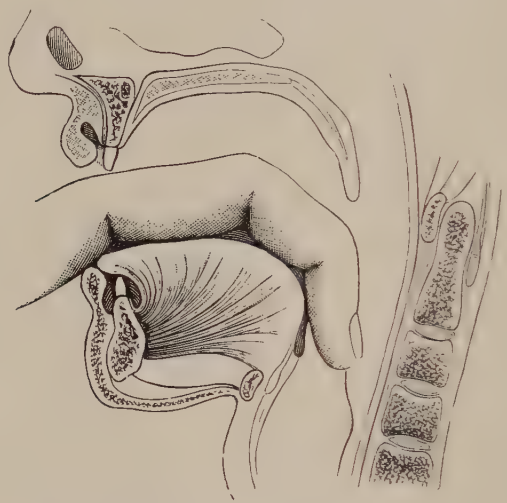


FIG. 139.—Fixation of the larynx. (Lejars.)

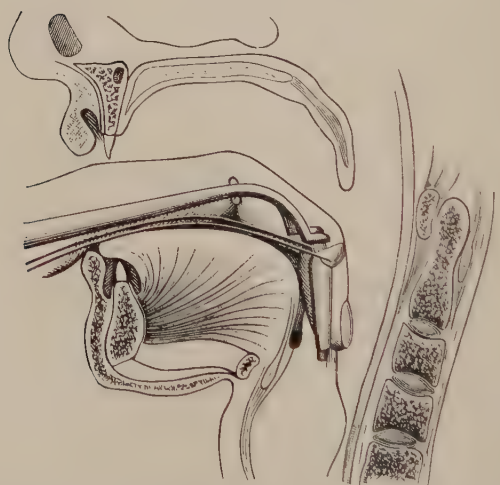


FIG. 140.—The tube guided by the index finger. (Lejars.)

delay the sensitiveness of the parts soon becomes so blunted that cough, on which the safety of the patient depends, is not excited, and death speedily results from suffocation.

The inexperienced and clumsy operator may incur other dangers,

such as asphyxia from prolonged attempts at intubation, lacerating the tissues, or forcing the tube into a false passage. All of these accidents can be avoided with care.

There are but few serious difficulties liable to be encountered by the experienced operator. It has been said that the tube may be obstructed

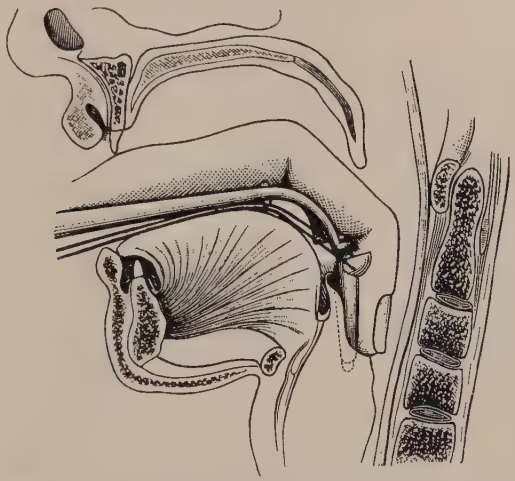


FIG. 141.—The tube penetrates the larynx. (Lejars.)

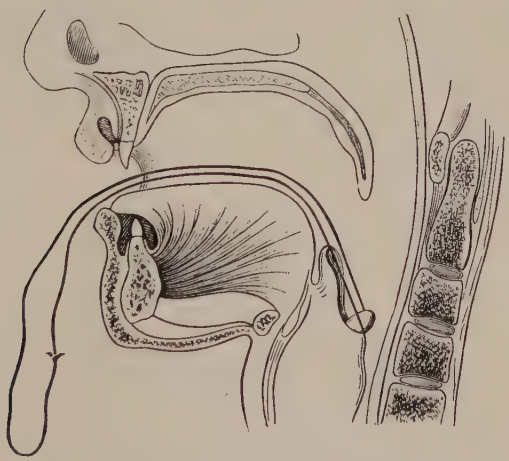


FIG. 142.—The tube in its proper position. (Lejars.)

in its course by entering one of the ventricles of the larynx. This, we are sure, hardly ever happens with the O'Dwyer tubes, which are so nicely rounded at their ends. Besides the pushing down of membrane before the tube, or the occurrence of a slight spasm of the muscles of the larynx, as described above, in introducing the tube the operator

will sometimes meet with difficulty caused by swelling, inflammatory thickening, or edema of the subglottic tissues. When it is found that the tube adapted to the age of the child will not enter readily it is advisable to try a smaller one. After this has been worn for a short time there is usually no difficulty in introducing one of the proper size. The narrowest part of the lumen of the larynx is in the region of the cricoid cartilage. We have seen a few instances in girls in which the cricoid ring was abnormally small, a fact which we have been able to demonstrate *postmortem*. When this condition exists only a little swelling or edema of the lining membrane is needed to make the introduction of the tube difficult. The only thing to do in such cases is to use a smaller tube.

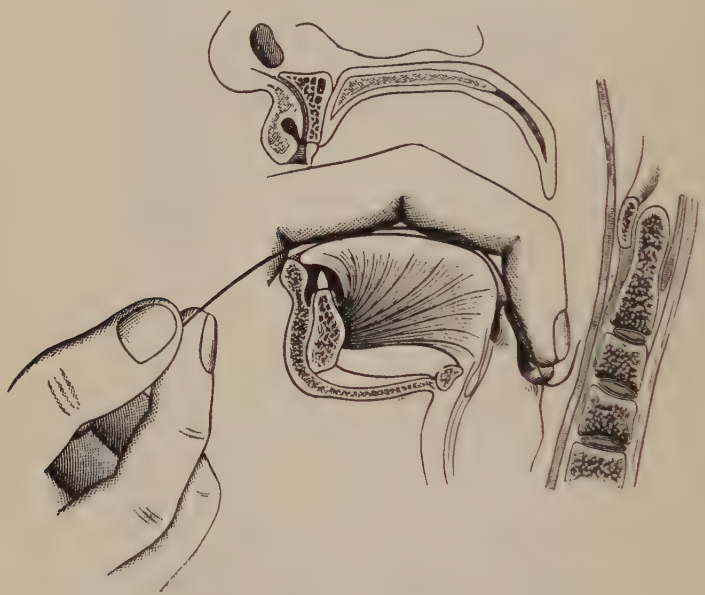


Fig. 143.—Withdrawal of the thread. (Lejars.)

Treatment and Feeding After Intubation.—It is advisable not to make any local applications to the throat while the tube is in the larynx; at least, irrigation or spraying should not be practised. The applications to the nose, if required, need not be omitted. Internal treatment, stimulants and the like may be continued as before.

The feeding of the child is the thing that frequently gives us the most concern. Some children swallow with but little difficulty after intubation, while it is really distressing to see others drinking liquids of any kind. The act of swallowing excites coughing, and this may be still further excited by some of the liquid running down the tube into the trachea. The cough is often violent, causing a large part of the liquid

in each act of swallowing to be forcibly expelled, not only through the mouth but through the nose also. Children, however, usually persevere in drinking, and after a little while they frequently get along better. Semi-solid food is not so liable to cause coughing, and is, therefore, preferable. When a child is old enough, we prefer to have it fed on bread soaked in milk. This forms a bolus which can be swallowed, as a rule, without exciting much cough.

FIG. 144.—Casselberry's position for feeding intubated cases. (After Northrup.)

It is claimed that the difficulty of swallowing, even of liquids, may be overcome by placing the child on its back with the body and legs elevated, while the head hangs over backward at an angle of 45 degrees or greater. It is thought that any liquid that may get into the tube will, with the child in this position, run out again rather than into the trachea. The placing of the child in this position during feeding was first recommended by Casselberry, of Chicago. He and many other physicians who have tried this method speak of it very favorably. In our experience it has not proved so satisfactory. In bottle-fed babies it sometimes answers fairly well. It should be stated that some physicians believe that the child swallows better lying on the abdomen with the head hanging forward.

If it be found that the child is not getting sufficient nourishment by either of the methods mentioned, gavage should be resorted to. This may be done by introducing either a small esophageal tube or a flexible catheter through the nose into the stomach. If this route is found inconvenient or difficult the child's jaws may be slightly separated and

the tube introduced through the mouth. If one catheter should not be long enough another may be joined to it by means of a short glass tube. Some prefer rectal feeding, but we have never found it satisfactory.

Removal of the Tube, or Extubation.—The time for removing the tube will depend very much on the age of the child and the stage of the disease. In older children the tube may be removed earlier than in those who are younger. Likewise, when the tube is not required until a late stage of diphtheria, it may be removed sooner than when introduced at an early stage of the disease. We have seen it stated somewhere that O'Dwyer recommended that the average time of wearing the tube should be seven days; if the patient's residence is a long distance from the physician's office the time had better be eight days. It has been our rule to allow the tube to remain in place six days before removing it. Frequently, however, the resident physicians remove it earlier, but they often find it necessary to reintroduce it. Northrup thinks that five days for a child over two years of age is long enough for the tube to be worn in the average case, since the time required is materially reduced by the administration of antitoxin.

Cases are not infrequently seen in which the tube, after having been worn for only a short time, is coughed up and expelled, together with a mass of membrane. Such cases sometimes recover without reintubation being required. There are other cases in which the tube is not retained longer than it is needed; that is to say, in the course of four or five days, when the membrane in the larynx has disappeared and the edema subsided, auto-extubation takes place through the agency of the cough. This result is always gratifying, and especially so to the inexperienced operator.

Whenever the tube becomes obstructed it must, of course, be instantly removed. Fortunately, in most cases it is coughed up. When coughed up the tube is either expelled or the child removes it from the mouth with his fingers. In rare instances it is swallowed. Should this occur, no great uneasiness need be felt, as we have never known a tube that was swallowed fail to pass through the intestines.

Up to a certain point the technique of the operation of extubation is exactly the same as that of intubation. After being rolled up in a blanket or sheet, as before, the child should be held in the upright position on the lap of the nurse, or placed in the dorsal position, according to the choice of the operator. It is equally important that the child's head should be held steady, and that the axis of the head, neck and trunk should correspond. The mouth gag being in position, the operator passes his index finger of the left hand backward over the dorsum of the tongue until he feels the tube and determines its position. He should then tilt the epiglottis forward and control it. Holding the extractor in his right hand, with the handle of the instrument near the chest of the child, he should pass it backward along the side of the finger until the tube is reached; the handle of the

extractor should then be raised to a horizontal position, and, with the aid of the tip of the finger which is controlling the epiglottis, he inserts the beak of the instrument into the opening of the tube. Having succeeded in doing this, he presses down the lever at the upper part of the extractor with his thumb, which causes the two parts of the beak of the instrument to separate, and thus the tube is caught and held, very much as a glove stretcher holds the finger of a glove. The operation is completed by lifting the extractor with the tube until it impinges on the hard palate, then depressing the handle and withdrawing the instrument and tube from the mouth. If the tube should slip off, as it often does, after having been lifted from the larynx, its removal can easily be concluded by means of the finger.

It is important to properly regulate the distance of separation of the two parts of the beak of the extractor. This may be done by means of the screw in the handle. If the jaws of the instrument are allowed to open too widely the orifice of the larynx may be lacerated by a clumsy operator. The extractor should be held in the hand lightly, as no great force is required to remove the tube. Be careful not to place the thumb on the lever until the beak of the instrument is well within the opening of the tube. If the operator should have difficulty in grasping the tube, it is better to make repeated short attempts, allowing the child to rest for a minute or two in the intervals, than to make a single prolonged effort.

After the tube has been removed the patient should be placed in bed and carefully watched for a while to see that the respirations continue easy. In family practice the physician should not leave the house for at least thirty minutes. If there is any difficulty in breathing he should remain until he feels reasonably sure that the patient is going to get along without the tube. Reintubation is often necessary. When dyspnea returns after extubation the condition of the patient not infrequently becomes critical so quickly that if prompt aid be not afforded death from suffocation will surely result. It is, therefore, highly important that the physician should be within easy call for some hours. Having seen not a few children perish at this stage of the disease when their lives might have been saved by prompt aid, we feel that the importance of the advice just given cannot be emphasized too strongly. To lose a child during the height of an attack of membranous croup is bad enough, but to see it die after the danger has apparently passed, and when the brightest hopes are entertained for its recovery, is much worse. Such a result may not inaptly be compared to the sinking of a ship in the harbor after it has weathered the storms of the ocean.

For lessening the nervous excitability of the patient, as well as for its relaxing effect, a little morphine may be given just before removing the tube, and an ice-bag applied to the larynx. It is sought in this way to lessen the irritation and swelling of the larynx. The child is still kept in a recumbent position for one or two days. Perfect quiet-

ness at this time is of great importance. A few hours of quiet sleep after extubation is quite desirable, as it will sometimes tide a patient over the period at which the indications for reintubation are most likely to develop.

Prolonged Intubation.—Despite the free use of antitoxin, and the greatest possible care in the operation of intubation and extubation, it frequently happens that the tube must be worn for a much longer period than five or six days. In other words, when the tube is removed at the time just indicated the dyspnea returns, making reintubation necessary, and this sometimes happens over and over again in the same patient through a long series of intubations and extubations. We know of nothing connected with the work of intubation that is more perplexing to the operator, or more distressing to the patient, than this unfortunate occurrence. Some of these cases require months and in rare instances years of intubating until recovery takes place. Indeed, a large proportion of the most obstinate cases perish from one cause or another before the difficulty is overcome.

Prolonged intubation is not always due to the same cause; it may result from one of several causes, such as persistence of the false membrane in the larynx, edema of the tissues, subglottic laryngitis with thickening of the soft parts, ulcerations, exuberant granulations, cicatricial contractions, destruction of the cartilages and collapse of the larynx, atony of certain muscles or abductor paralysis. But it must be admitted that it is often difficult to differentiate between these various pathological conditions of the larynx, or to explain satisfactorily the exact cause of the difficulty.

Some writers believe that the conditions rendering the prolonged use of the tube necessary are rare, or even extremely infrequent. We have met with very many cases in which it was necessary to continue the use of the tube longer than the usual period of five or six days without development of the pathological changes which lead to chronic stenosis. Such cases are able to get along without the tube in the course of two weeks, or three, at the longest. But postdiphtheritic stenosis occurs, according to our experience, in from 1 to 3 per cent of all cases of intubation. Dillon Brown is reported as saying that he has encountered it in the proportion of about once in 75 or 100 cases.

In discussing the causes of prolonged intubation but little consideration need be given to traumatism resulting from the introduction or removal of the tube. While it is true that the unskilful use of the introducer or extractor, or too much pulling upon the epiglottis during the operation, may cause abrasions and edema of the soft parts, and thus make reintubation necessary, yet it is certain that the principal cause of "retained tubes" is not due to such an injury, but to traumatism in the larynx occasioned by the tube itself. It is important that the tube should properly fit the larynx; it certainly should not be too large. But no matter how well it fits, it sometimes causes ulceration. It should, therefore, be dispensed with as soon as possible.

It, however, should not be removed until there is reason to believe the patient can get along without it; for removing it too early would necessitate its reintroduction, and thus the risk of traumatism would be increased.

When the tube is required longer than the usual length of time on account of the persistence of false membrane in the larynx, the condition, from our present point of view, is not serious, for as soon as the membrane disappears the tube can be dispensed with.

We believe that the most common cause for retention of the tube, at least primarily, is subglottic laryngitis with edema. Later, as the tube is worn longer, and has been removed and reintroduced many times, tissue changes of a destructive character sometimes take place in the larynx, with a marked tendency to terminate in chronic stenosis. We have removed, *postmortem*, larynges which showed considerable loss of tissue from ulcerative action. These ulcers heal by granulation and the formation of cicatricial tissue, and hence permanent stenosis to a greater or less degree is liable to result in such cases.

Many of the cases with subglottic laryngitis and edema improve after two or three intubations, and recovery follows without any untoward symptoms. Other cases are more troublesome, especially those which develop also atony of the muscles or abductor paralysis. With this complication it may be necessary to repeat intubation many times, and the patient is fortunate if he escapes ulceration of the larynx. He, however, rarely escapes bronchopneumonia, more or less marked.

When there is marked ulceration of any part of the larynx, with little or no edema, the child may get along fairly well without the tube for a few days, but as cicatrization takes place the lumen of the larynx becomes gradually diminished, with a corresponding increase of dyspnea. In attempting to perform intubation in such a case it has been found impossible to introduce the tube. We have been confronted with this difficulty more than once, and in order to save the child's life have resorted to tracheotomy.

In cases of ulceration of the larynx we believe it is good practice to use the tube intermittingly until the ulcers have cicatrized. If there is difficulty in introducing the tube it had better be left undisturbed for a long time, *i. e.*, from one to two weeks at least. In cicatricial stenosis, however, after the difficulty is overcome of introducing a tube, though small, but of sufficient caliber to supply the lungs with air, it is comparatively easy, after this tube has been worn for a day or two, to introduce a larger one. Having thus restored the normal lumen of the larynx, it is advisable to insert the tube two or three times a week for a while, leaving it in place from twelve to twenty-four hours. Later, as the conditions improve, it need not be introduced so frequently. But the tube should not be dispensed with until the tendency to recontraction of the cicatricial tissue has been overcome.

In cases of prolonged intubation the vulcanite tube should by all means be preferred. The calcareous deposits which always form on

metallic tubes make them very objectionable. They cannot be worn long without causing irritation and often ulceration of the larynx. As these deposits do not form on hard-rubber tubes, they may be allowed to remain in position for a long time without doing harm. One of our cases of four years' standing has worn a vulcanite tube continuously for periods of three months each, and once as long as five months, without removal, with no unpleasant consequence except, as the parents say, an offensive breath. The tube never showed any calcareous deposits. It is worthy of remark that when the tube has been worn for a long time the child acquires the ability to swallow with little or no difficulty.

We have called attention to the fact that in some cases of prolonged intubation, after the tube has been removed for a few days, it is impossible to reintroduce it, and that *tracheotomy* becomes necessary. Likewise, this operation may be deemed expedient when the tube cannot be retained in position. We have seen cases in which the tube was constantly coughed up, even when it was two or three sizes too large. In such a case it sometimes happens that the head of the tube enters the postnasal space and suffocation threatens if the tube be not immediately removed or pushed down into the larynx. To keep it in place would require a constant attendant. Under such circumstances it is better to perform tracheotomy.

In this troublesome class of cases we are, however, reluctant to recommend tracheotomy except as a *dernier ressort*. This is because of the difficulty we have many times experienced in getting rid of a retained tracheal cannula.

After returning to their homes, 3 of our patients of this description were taken to a general hospital in Philadelphia and placed under the care of a surgeon. An operation was performed with the view of overcoming the stenosis due to contraction of the cicatricial tissue in the larynx, but in each instance the operation was unsuccessful, and the tracheal cannula had to be continued. Two of these unfortunate children subsequently contracted pneumonia and died.

The difficulty in getting rid of the tracheal cannula in this class of cases may not be due alone to cicatricial tissue in the larynx caused by the intubation tube. In addition to this a later obstruction is not infrequently developed as the direct result of the inflammation caused by the long-retained cannula. This occurs at the upper angle of the wound, and may be in the nature of a stricture, or the larynx may be completely occluded by cicatricial tissue. This condition is even of more serious import than the former. We have seen 2 such cases in which it was impossible to pass a probe through the lumen of the larynx, either by way of the mouth or the tracheal wound, and the voice, even in the faintest whisper, was lost, which proved that no air passed through the larynx. According to O'Dwyer, a stricture of this description develops in a large proportion of young subjects when the operation is high, involving the cricoid cartilage or its immediate

vicinity. He says: "When the wound is still higher, that is, wholly within the larynx, complete occlusion with adhesion of the vocal cords is very liable to occur," etc.

As to the treatment of chronic stenosis of the larynx, we believe that long-continued intubation offers the best results. As soon as the tube is once introduced, no matter how small it may be, the chief difficulty is overcome. After this, tubes of graduated sizes should be employed, one after the other, until the one suited to the age of the child is reached. As already stated, the tube may have to be worn intermittingly for a very long time before the cicatricial tissue loses its power to contract. The physician should not become discouraged too soon, but persevere, as it may sometimes require years to remedy the difficulty.

When occlusion of the larynx is complete, or nearly so, whether caused by the intubation tube or a long-retained tracheal cannula, it will be found impossible to introduce a croup tube of the smallest size. Such cases are difficult of management by the general practitioner, and had better be referred to the laryngologist. We believe, however, that instead of attempting to force an entrance from above downward, it is better to etherize the patient and enlarge the tracheal wound at its upper angle so as to admit of the introduction of a sound from below. In this way the sound is less liable to injure the parts by catching in the ventricles. The intubation tube should then be introduced and worn continuously for one or two weeks, after which it should be employed intermittingly until a cure is effected. This procedure was recommended by O'Dwyer in a paper read before the British Medical Association in 1894, on "Treatment of Chronic Stenosis of the Larynx by Intubation." In this paper O'Dwyer says: "The length of time that intermittent intubation will be required to effect a permanent cure will be influenced largely by the amount of cicatricial tissue present and its location. If confined to the chink a more speedy result may be expected, because of the stretching which is exerted by the expansion of the glottis with every breath. After the normal lumen of the larynx has been restored, or at least ample breathing room secured, a tube should be inserted once or twice a week, and allowed to remain in position from twelve to twenty-four hours. This interval can be gradually increased according to indications, and continued until the tendency to recontraction has been permanently overcome."

After the introduction of the intubation tube in these cases of chronic stenosis in which tracheotomy has been performed, it is desirable that the tracheal wound should be kept open for some time. If it could be kept patulous —a thing difficult to accomplish in a child —the liability of the tube being coughed out would be greatly lessened. A special tube or combination of tubes that would meet this indication seems to be an important desideratum. At any rate, O'Dwyer's advice should be heeded. It is as follows: "In practising intubation for the removal of a tracheal cannula, the wound under all circumstances must be kept

open until sufficient breathing room through the natural passage has been secured to sustain life, in case the tube should be coughed out. This is, as a rule, extremely difficult to accomplish, especially in children. The hard-rubber plug devised by Drs. Pitts and Brook, and used in a series of cases, appears to be most practicable for this purpose. It is provided with a collar similar to that on a tracheal cannula, by which it can be held in position."

TREATMENT OF CARRIERS.

There is no practical problem in the management of diphtheria more difficult than the treatment of carriers of virulent bacilli, and particularly in relation to quarantine and public health. Prolonged quarantine after recovery is always irksome to both physician and patient as well as expensive and especially for hospitals for the treatment of the acute infectious diseases.

A large number of methods for treatment have been advocated from time to time, but none can be said to be satisfactory. It is true that some result in a *temporary* masking of the carrier state resulting in two or three consecutive negative cultures, but in many instances cultures at the end of a week or two are again positive.

In handling such cases it is first necessary or advisable to determine whether or not the bacilli are virulent. For this purpose the guinea-pig test is to be recommended as a reliable procedure when properly conducted with *several colonies* of diphtheria bacilli in order to avoid the error of conducting it with a non-virulent strain while overlooking the presence of virulent organisms. Carriers of non-virulent bacilli may be released, but this decision is permissible only after very carefully conducted virulence tests.

The administration of antitoxin and its local application to the tissues is without avail.

Spraying the parts with live cultures of staphylococci or lactic acid bacilli sometimes masks the carrier state for varying periods of time but is otherwise ineffectual.

Vaccine treatment has been advocated by Hewlett and Nankwell,[1] Fraser and Duncan[2] and others. The latter prepare a detoxicated vaccine carrying 100,000,000,000 per cubic centimeter and give an injection every four days for 12 injections, beginning with 0.05 cc. and increasing until as much as 3.5 cc. is given on the last injection. We have had no experience with this method.

Churchman and Herz[3] and Saurman[4] have employed solutions of gentian violet, a 2 per cent solution being thoroughly applied by spraying four times a day after preliminary cleansing with saline solution. The staining of the tissues and teeth is temporary. Kolmer, Woody and Yagle[5] and Browning[6] have also tried 1 to 250 solutions

[1] Lancet, 1912, i, 143.
[2] Lancet, 1920, ii, 994.
[3] Jour. Exper. Med., 1913, **18**, 579.
[4] Jour. Am. Med. Assn., 1924, **83**, 249.
[5] Jour. Infect. Dis., 1920, **26**, 179.
[6] Applied Bacteriology, 1918, p. 87.

of brilliant green. Both dyes are highly destructive for diphtheria bacilli but the effects in the treatment of carriers have been usually only temporary, since almost always cultures over one or two weeks of time have shown the presence of bacilli. Gray and Meyer[1] have advocated applications of 0.5 to 2 per cent solutions of mercurochrome, but this too, has failed in our hands.

Longabaugh[2] has advocated the inhalation of ether by the open method for about five minutes every morning followed by culturing, sufficient being given to produce marked drowsiness. Israeli[3] used a 10 per cent ichthyol ointment introduced into both nasal cavities to the naso-pharynx on each of five days in succession for the treatment of nasal carriers.

Tonsillectomy appears to be the only method of real value, but of course it is not always possible to obtain consent and especially since a cure cannot be guaranteed; furthermore, it is of no use in the treatment of nasal and postnasal carriers.

Hicken,[4] Kahn[5] and Withers, Ranson, and Humphreys[6] have advocated treatment with roentgen-ray in selected cases. The last mentioned state that all radiation was given at 50 cm. target skin distance and filtered through 0.75 mm. of copper and 1 mm. of aluminum. In no case was more than 60 per cent of an erythema skin dose given, which was just sufficient for producing some dryness of the mouth. As a rule, the treatment was given at the rate of 50 to 100 milliampére minutes to each side of the head, weekly. The results were summarized as follows: "If the experimental cases and those patients having foci of infection other than the pharyngeal lymphoid tissue are eliminated, there are left 17 patients who were positive in an average of 49.7 days who became negative and remained negative in an average of 9.5 days after the first roentgen-ray treatment was given. In the carriers, of which there were 42, all but 3 became negative during the three months' observation period. This is a percentage of 85. If those carriers who had experimental small doses of roentgen-ray are eliminated and those with a complicating pathological condition also are disregarded, there are left 23 carriers with an average positive culture period of 60.9 days who became negative in an average of 10.9 days after the first roentgen-ray treatment."

It would appear that this method is worthy of further trial; up to the present time, however, we have had no experience with it.

[1] Jour. Infect. Dis., 1921, **28**, 323.
[2] United States Naval Med. Bull., 1924, **21**, 190.
[3] Jour. Lab. and Clin. Med., 1925, **10**, 536.
[4] Am. Jour. Roentgenol., 1922, **9**, 319.
[5] Ibid., 1924, **13**, 343.
[6] Jour. Am. Med. Assn., 1927, **87**, 1266.

CHAPTER XVII.

SERUM ANAPHYLAXIS.

With the advent of antitoxin treatment of diphtheria in 1894 the injection of immune horse serum quickly became a common practice in the treatment of disease; almost immediately cases of untoward effects were observed and reported, although occasional cases were previously recorded following transfusion with lamb's blood. Among the earliest cases of serum disease following the injection of diphtheria antitoxin was the immediate and fatal attack of a son of Professor Langerhans. This case created a profound impression upon the medical profession, and at the present time many physicians, fearing anaphylaxis, hesitate to administer diphtheria antitoxin and other sera for prophylactic and therpeutic purposes, these fears being shared by many of the laity.

Types of Sero-anaphylactic Reactions. -An immediate reaction rarely follows the first injection of serum unless the patient is one of those unfortunate but rare persons who in some manner have been rendered highly sensitive to horse protein. In the majority of instances symptoms do not develop for from eight to twelve days, during which time the antibody is being produced; this is the usual *delayed reaction*. When antibody formation has reached a certain point it reacts upon any of the horse serum that may persist in the cells or circulation, producing the anaphylactic reaction. If the dose of serum has been small antibody formation goes on as usual, but the serum may not persist in the circulation. Hence symptoms do not develop in such a person, although if reinjected subsequently symptoms will appear. This is one reason why a concentrated serum is not so likely to produce serum sickness, since a smaller quantity of it is injected.

If, however, the patient has received an injection of serum some months previously, a reinjection is likely to be followed by an *immediate* reaction, that is, the symptoms appear within from a few minutes to twenty-four to forty-eight hours. If the first injection had been given a year or more previously no antibody may be present in the blood, so that an immediate reaction does not occur. If, however, the cells once stimulated are "keyed up" indefinitely, and, accordingly, antibody formation is quite rapid, so that we find symptoms developing in from four to seven days after injection the *accelerated reaction*. Or a small amount of antibody may be present which gives a mild reaction around the site of serum injection, followed in from four to seven days by a general reaction, this being *immediately followed by the accelerated reaction*.

As was previously stated, anaphylaxis is specific, that is, a person

receiving ox serum in the first injection would not be affected subsequently by an injection of horse serum, but only by ox serum. For this reason it has been recommended that diphtheria antitoxin to be used for prophylactic purposes should be prepared by immunizing cattle, reserving the horse serum for treatment if the disease should be contracted subsequently.

The Nature of Serum Disease or Serum Sickness.—Inasmuch as the reactions followed the injection of horse serum, the condition became known as "serum disease."

This name was applied by von Pirquet and Schick[1] to the *various clinical manifestations, such as eruptions, fever, edema and pain in the the joints, following the injection of horse serum.* These symptoms are due to the horse serum itself, for, as was early shown by Johannessen,[2] Bokay[3] and others, they may manifest themselves after the injection of sterile normal horse serum. The serum, moreover, of certain horses appears to be more likely than that of others to cause these symptoms, thus accounting for the fact that one lot of antitoxin will cause a higher percentage of serum sickness than will another. Concentrated serum is not so likely to produce serum sickness as whole serum, owing partly to the fact that smaller doses of it are given. According to Rolleston and Ker, the frequency of serum sickness is, as a rule, in direct proportion to the amount of serum given, and in inverse ratio to the severity of the attack of diphtheria; in other words, we may expect to encounter it most often in mild and moderately severe cases that have received very liberal dosages of serum.

Serum sickness is regarded as a true anaphylactic phenomenon. We are prone to call the severe, fatal and rare instances of death following serum injection examples of anaphylaxis, and to regard serum sickness as a different condition. Both are fundamentally the same, except that in the first instance the body cells are for some unknown reason unduly and highly anaphylactic. *Fortunately, this undue hypersensitiveness is frequently foreshadowed by the asthmatic or hay-fever-like attacks which the susceptible person may exhibit when he enters stables or is otherwise around horses. It goes without saying that horse serum should never be given to such persons.*

While serum sickness is usually due to horse serum for the reason that the horse is so commonly employed in the preparation of various curative serums, the serum of the ox, rabbit and other animals may induce the same train of symptoms in addition, in some instances, to producing a direct toxic effect.

Relation of Route of Administration of Serum to Anaphylactic Reactions.—The route by which serum is administered to man bears a very important relation to both the severity and time of appearance of the symptoms of anaphylaxis.

[1] Die Serumkrankheit, Leipsic, Deuticke, 1905.
[2] Deutsch. med. Wchnschr., 1895, **21**, 855.
[3] Jahrb. f. Kinderh., 1897, **44**, 133.

Acute anaphylactic shock of the lower animals is produced by the *sudden* introduction of serum into sensitized animals by intravenous injections. The same is true of human beings. The intravenous and subarachnoid injections of serum produce anaphylactic effects more quickly than intramuscular and subcutaneous injections, while internal administration by mouth or colonic injection are least likely of all to produce these effects.

With those exceptional human beings who are very highly sensitized to horse protein, as the "horse asthmatics," even the subcutaneous injection of serum may result in an immediate reaction developing within a few minutes, but with the great majority of persons the subcutaneous or intramuscular injection of horse serum is followed by a period of several days to two weeks or more before the onset of symptoms.

Relation of Amount of Serum Administered to Anaphylactic Reactions.—Ordinarily the administration of purified or concentrated serum does not produce as high an incidence of serum sickness as whole serum. Horse serum contains at least three sensitinogens—euglobulin, pseudo-globulin and albumin. Concentrated antitoxin sera prepared by the Gibson-Banzhof method is composed largely of the pseudo-globulins which carry most of the antitoxin; the employment of these concentrated sera means that there is a reduction of the total protein in relation to the antitoxic value and the elimination of all or most of the euglobulins and albumins lessens very materially the chances of inducing serum sickness and the production of recurrent eruptions.

Even the whole serum, smaller amounts, injected subcutaneously or intramuscularly, are less likely to produce serum sickness than larger amounts. With intravenous injections there is less relation and among "horse asthmatics" a few centimeters by any route may induce as much reaction as larger amounts.

Danger of Anaphylactic Reactions.—The occurrence of immediate reactions and fatalities after the administration of horse immune sera employed for prophylactic and curative purposes has unduly impressed many physicians and engendered a fear of producing reactions which is shared by many of the laity; one result has been hesitation in the administration of diphtheria and tetanus antitoxins for the prophylaxis and treatment of these infections. For this reason a general and brief statement on the dangers of anaphylaxis in man may be in order:

1. Bearing in mind that thousands upon thousands of injections of horse-immune sera, and especially diphtheria and tetanus antitoxins, are administered throughout the world each year; the incidence of *fatal* anaphylactic reaction is very small (probably about 1 in 50,000 to 100,000 injections). The exact incidence cannot be stated because not all cases are recorded, but several investigators have reported the absence of fatal reactions in series as large as 200,000 injections. Furthermore, some of the fatalities attributed to the anaphylactic effects of the serum may have been caused by other factors. Approxi-

mately 70 fatalities after the administration of serum have been recorded.

The incidence of severe reactions during or immediately after the intravenous or subarachnoid injections of serum is much larger, but recovery is the rule. Likewise the incidence of mild anaphylaxis designated as "serum sickness" or "serum disease" is high, but this reaction is without danger.

2. Individuals, including children as well as adults, who are uncomfortable around horses, and are seized with sneezing, coughing, "asthma" or other hay-fever-like symptoms, are extremely sensitive to horse protein and should not receive injections of horse serum by any route. Apparently many of the small group of fatalities following the administration of serum have occurred among these persons. A physician called upon to administer serum should always first inquire upon this point; if the history is suggestive a skin test may be conducted, as described in a succeeding section. Desensitization may likewise be tried as described later, but in a typical "horse asthmatic" the administration of horse serum is dangerous despite these precautions.

Children with status thymolymphaticus are likewise bad risks; this condition is regarded by some investigators as responsible for some of the fatalities following the administration of serum.

3. Individuals who have received injections of serum upon a previous occasion are almost sure to develop "serum sickness" after reinjection, but this is not dangerous, although distressing, and should not be a contraindication to the use of serum. Serum may be administered by subcutaneous or intramuscular injection with safety, *but when given intravenously due care must be exercised,* since fatalities have occurred on rare occasions. Thus Jamson,[1] in a complete review of the literature up until 1924, found 8 reported cases, and since then Mendeloff[2] and Tuft[3] have reported 2 additional cases. Park,[4] however, is convinced, because of a large experience with second injections, that they are not dangerous, has reinjected a large number of cases, in spite of the presence of positive skin tests, and in no instance observed severe reactions.

When serum is given intravenously to such individuals preliminary desensitization should be practised. This is likewise advisable before the intraspinal injection of serum.

Symptoms of Immediate and Severe Anaphylactic Shock.—These are characterized by sudden onset—often within a few minutes after or during the intravenous injection of serum. The patient becomes restless, anxious and may give an outcry; there is marked pallor, perspiration, rapid and feeble pulse. Respirations become deep, labored

[1] Jour. Am. Med. Assn., 1924, **82**, 1091.
[2] Ibid., 1862.
[3] Am. Jour. Med. Sci., 1928, **165**, 253.
[4] Jour. Immunol., 1924, **9**, 17.

and sometimes rapid, and the patient may become unconscious. Muscular twitchings, rigors and convulsions may occur with micturition and defecation. In rare instances death occurs during coma with respiratory failure, while the heart is still beating.

Some of these symptoms may develop during the intravenous injection of serum, but subside as soon as the injection is stopped. Death does not occur except in those rare cases of extreme sensitization to horse protein; in these even the subcutaneous injection of serum may bring on the reaction with a fatal outcome.

Not infrequently a reaction of fever, chills, rapid pulse and prostration develop an hour or two after the intravenous injection of serum; this reaction is probably not anaphylactic, but protein shock.

Symptoms of the Usual Reaction (Serum Disease).—*The most typical of these symptoms are rash, fever and prostration, besides joint and muscle pains, edema and adenitis.*

These symptoms and lesions may develop within a few hours to two weeks or so after the intravenous, intraspinal, intramuscular or subcutaneous injection of serum. In the majority of cases the reaction develops eight to twelve days after the injection, although it may appear within the first few days and especially if the individual had received an injection of serum on a previous occasion.

Frequency.—The frequency of these reactions varies greatly in the different recorded series of cases. It would appear that the incidence in Germany (8.1 per cent) and France is much lower than in America. The incidence in this country has varied with the sera of different horses and has been generally lower with concentrated (purified) sera than with whole sera.

Reactions are slightly more frequent after intrathecal injections of serum than after subcutaneous injections. The following table gives the approximate incidence from different parts of the world:

Incidence of Serum Disease.

Reported by.	Route of administration.	Serum.	Incidence, per cent.
Flexner	Intrathecal	Whole	70.0
Rolleston	Intrathecal	Whole	40 to 61
Drought	Intrathecal	Whole	55.0
Goodall	Subcutaneous	Whole	35 to 40
Hartung	Subcutaneous	Whole	11.4
Rolleston	Subcutaneous	Whole	44.0
Dant	Subcutaneous	Whole	11.4
Coca	Subcutaneous	Purified	8.5
Kolmer	Subcutaneous	Purified	10.0

In a general way it may be stated that the administration of *whole horse serum* by subcutaneous, intramuscular, intravenous and intrathecal injection is followed by serum disease in 40 to 60 per cent of cases; the subcutaneous or intramuscular injection of *purified horse-antitoxin serum* is followed by serum disease in approximately 10 per cent of cases.

Incubation Period.—Symptoms may appear in fifteen minutes after the intravenous injection of whole serum. In about 10 per cent of cases developing serum sickness the symptoms appear within the first four days; the majority (about 60 per cent) of cases develop symptoms in from six to ten days after injection, and these are the critical days.

Fever.—After the intravenous injection of serum a thermal reaction may develop within one hour or two, but this is usually due to non-specific protein shock rather than to anaphylaxis. In serum disease the temperature usually rises one or two days before the rash or on the same day just as the rash appears; it is well for the physician to keep this in mind in order to guard against concluding that this fever is due to reinfection or exacerbation of infection. Sometimes fever is absent and especially in mild cases.

Eruption.—The most obvious and important of the symptoms are undoubtedly the various forms of *rash*. In 1000 consecutive cases of diphtheria treated with antitoxin in the Philadelphia Hospital for Contagious Disease a rash developed in 430, or 43 per cent. The time of appearance of the eruption depends, as was just stated, upon whether or not the patient has been injected on a previous occasion, and, if so, the length of the interval between the first and subsequent injection, and to a lesser extent upon the amount of the first injection, these factors influencing the quantity of antibody present at the time reinjection. About 63 per cent of cases develop a rash between the sixth and the ninth day after the injection of antitoxin, as shown in the following table:

TIME OF APPEARANCE OF SERUM RASH IN 430 CASES OF SERUM DISEASE.

Day upon which rash appeared after injection of diphtheria antitoxin.	Total number showing rash.	Percentage.
First	4	0.9
Second	6	1.4
Third	7	1.6
Fourth	30	6.9
Fifth	35	8.1
Sixth	75	17.6
Seventh	65	15.1
Eighth	85	19.8
Ninth	44	10.2
Tenth	39	9.0
Eleventh	22	5.1
Twelfth	5	1.1
Thirteenth	6	1.4
Fourteenth	5	1.1
Fifteenth	1	0.2
Sixteenth	1	0.2

Three main types of rashes are generally recognized:

1. **Urticarial Rashes.**—If we include in this group all eruptions that present a resemblance to urticaria these rashes are the most common, constituting from 70 to 90 per cent of all eruptions. They usually appear after the seventh day, becoming manifest first about the site of injection. Large irregularly shaped and scattered blotches appear,

FIG. 145.—Antitoxin eruption following use of diphtheria serum.

FIG. 146.—Gangrene of skin after injection of diphtheria antitoxin. (Extremely rare occurrence; indeed, unique in our experience.)

FIG. 147.—Antitoxin eruption. Diphtheria subject.

FIG. 148.—Antitoxin eruption. Diphtheria subject.

frequently with true wheals in the center accompanied by intense itching and irritation. Sometimes true wheals do not appear. The rash is often very profuse, and fresh blotches may continue to appear for two or three days. Occasionally the rash is quite sparse and mild, and may disappear within twenty-four hours.

2. **Multiforme Rashes.** This type of rash is quite common. It is often circinate in its arrangement, or occurs in large blotches mixed

FIG. 149.—An unusual antitoxin eruption exhibiting erythematous patches on the trunk and vesicular lesions on the face.

with a scattered morbilliform or measly form of rash. Different parts of the body may present different appearances at the same time. This rash may occasionally closely simulate true measles, especially since it involves the face, and as the conjunctivæ are likely to be congested in almost any variety of serum sickness. It is differentiated from measles by the fact that Koplik's spots are absent, there is no prodromal rise in temperature, the papules are not elevated above the

skin as much as in measles and that the eruption frequently starts from the site of injection, instead of on the face.

3. **Scarlatiniform Rashes.**—This type of rash occasionally occurs, and may bear so close a resemblance to true scarlet fever as to be indistinguishable from it. The eruption usually appears early, that is, in from the first to the sixth day after injection, and may vary from a uniform erythema which *first appears about the site of injection* to a true punctate scarlatinal rash. The differentiation of these rashes

FIG. 150.—The same patient as Fig. 149, showing the vesicular character of the lesions on the face.

from the true scarlet fever eruption is one of the greatest sources of trouble in hospital practice, especially when they develop in the diphtheria wards, where occasional cases of true scarlet fever are always likely to appear from time to time. The absence of the following symptoms, or their occurrence only in mild degree, would favor a diagnosis of serum disease: Fever, or, at least, the presence of but a mild pyrexia, the vomiting, the typically furred tongue, the angina, or at least but a mild throat involvement, and the leukocytic inclusion

bodies—all forming the symptom-complex of true scarlatina. In many instances, however, it is necessary to isolate the patient when speedy recovery, absence of complications and less definite desquamation, which does not involve the palms and soles, indicate that the patient was suffering from serum disease and not from scarlet fever.

As previously stated, *the eruption is at first usually local about the site of injection of serum* and several days may elapse before it becomes generalized. In some mild cases the eruption remains localized. Recurrent eruptions sometimes occur. Occasionally there may be considerable edema present with the skin rash, or it may occur independently. It is most common about the face and neck and may be so extensive as to close the eyes; this usually lasts only a few hours.

Arthritis; Neuritis; Myalgia.—Painful and tender joints occur in about 2 per cent of cases. The process seems to be extra-articular; there is seldom any fluid in the joints, nor is the skin hot or reddened. There may be slight periarticular edema. Boots and Swift,[1] however, have recently stated that fluid was found in the joints of 4 of 6 cases studied, and that there were cytological changes of acute arthritis. Furthermore, horse serum was found in two fluids, suggesting "that the irritation of the joint may be due to the presence of this foreign protein in an allergic tissue." All the joints may be attacked or only one or two; the temporo-mandibular and metacarpo-phalangeal joints appear to be more frequently affected than other joints. Neuritis, myalgia and headache may also occur.

Adenitis.—The regional lymph glands, and especially those nearest the site of subcutaneous injection of serum, frequently become swollen and tender. These lesions are among the first to appear and first to disappear. Generalized adenitis may develop. Suppuration does not occur. Occasionally the cervical glands beneath the sterno-cleido-mastoid muscle may become so enlarged and tender as to suggest a pyogenic infection, but his usually disappears in two to three days. Occasionally the spleen becomes palpable.

Leukocyte Changes.—In the first few hours of serum disease there is likely to be a slight leukocytosis with an increase in the relative number of lymphocytes (30 to 40 per cent); this is followed by leukopenia. Frequently there is a slight increase of the eosinophile cells (3 to 7 per cent).

General Symptoms.—Tachycardia may occur even when the temperature is approximately normal. Diarrhea may develop and prove a troublesome symptom for several days. There is rarely nausea and vomiting. Marked prostration of the neuro-muscular system may occur followed by an asthenia of many days or weeks.

Mild nephritis with slight albuminuria is sometimes present. Longcope found about 10 per cent of cases showed albuminuria and casts. There is little change in the coefficient of urea excretion or in the

[1] Jour. Am. Med. Assn., 1923, **80**, 12.

phthalein output. The excretion of water and chlorides are rapidly diminished at the onset, but these renal changes are transitory and the return to normal is usually rapid.

Delahet[1] has described meningeal symptoms of anaphylactic nature following repeated intrathecal injections of serum.

Recurrent Serum Disease.—Mention has already been made of the "double reactions" of von Pirquet and Schick, the "accelerated" following the "immediate" reaction. A number of observers have reported second eruptions following in three to twenty-one days after the first eruption. Goodall[2] has described 2 cases of triple eruptions; in the first case the eruptions appeared on the first, third and seventh days, and in the second case they occurred on the second, seventh, and tenth days, following reinjection. Axenow[3] reports that of 683 cases of serum disease, 10 per cent developed a triple eruption and 2.3 per cent a quadruple eruption.

These recurrent eruptions appear to be caused by more than one sensitinogen in the serum; as reported by Coca they do not occur with the use of purified (concentrated) antitoxin sera.

Relation of Serum Sickness to Prognosis in Diphtheria.—Ronaldson,[4] in a study of 1000 cases of serum sickness in diphtheria, states that he has confirmed Rolleston's assertion that "The more marked the antitoxin reaction, the better is the prognosis." Increased dosage increased the incidence of serum manifestations, but diphtheria toxin exercises an inhibitory influence both on the frequency and the intensity of serum reactions. In very severe cases the rash is late in development, scanty or entirely absent. The presence of a rash, even of the most limited nature, is a favorable sign. A good rash suggests a good prognosis. A case with a well-marked reaction is not likely to end fatally, and the paralysis is unlikely. A primary rash is valueless in forming an estimate as to the likelihood of paralysis generally, its value being restricted to the severer forms. A secondary rash enables one to forecast with confidence that the patient will neither die nor suffer from paralysis of the graver types.

Skin Test for the Diagnosis of Serum Sensitization.—Anaphylactic phenomena can usually be expected to occur if serum is given within a year or so following a previous injection. Persons who experience discomfort when about horses should always be closely questioned. By means of skin tests the state of allergy to serum may be detected, and especially in those cases of extreme hypersensitiveness to horse protein. These preliminary tests are particularly indicated before the intravenous and intrathecal injection of serum when the patient is known to have had an injection of serum upon a former occasion. When serum is to be given subcutaneously or intramuscularly they are

[1] Bull. et mém. Soc. méd. d. hôp., 1920, **44**, 1272.
[2] Jour. Hyg., 1907, **7**, 607.
[3] Jahrb. f. Kinderh., 1913, **68**, 565.
[4] Brit. Jour. Child. Dis., 1923, **20**, 129.

not necessary unless the physician suspects that the patient is hypersensitive to horse protein.

If the individual is known or suspected to be extremely sensitive to the serum cutaneous tests should be done; otherwise the intracutaneous test is more sensitive and to be preferred when serum is to be given intravenously for therapeutic purposes.

For conducting the *cutaneous test* either raw normal or immune serum (not purified or concentrated antitoxins) or dried serum proteins may be employed.

Reactions develop within fifteen minutes as described; Plate XXVII shows the urticarial-like lesions that develop on the arm of one of our colleagues following scarification and the thorough application of a drop of horse serum. This man is also susceptible, to a less extent, to guinea-pig and rabbit serum, and is seized with sneezing and distressing dyspnea after entering a house where these animals are kept.

For *intracutaneous tests* sterile raw normal or immune serum (not purified or concentrated serum) should be diluted 1 to 50 with sterile saline solution and 0.1 cc. (= 0.002 cc. undiluted serum) injected intracutaneously; or, the dose injected may be larger, as 0.1 cc. of 1 to 5 dilution (0.02 cc. undiluted serum), if only a slight degree of hypersensitiveness is suspected. A small white wheal showing the little depressions of the hair follicles is produced. An injection of 0.1 cc. salt solution is made as a control.

If the test is negative the wheals produced by both serum and saline solution disappear in a few minutes. If sensitiveness exists a genuine urticarial wheal develops in five to ten minutes, which reaches its maximum within one hour and fades away within a few hours. General symptoms of flushing of the face, tachycardia, and difficult breathing develop, but rarely and only in cases of extreme hypersensitiveness.

Prevention of Sensitization. — No efficient method of preventing sensitization of human beings by horse serum has been discovered, although this is a very important problem worthy of investigation.

Besredka[1] states that heating therapeutic sera to 56° C. for an hour on four days in succession renders the serum less sensitizing. This method is practised at the Pasteur Institute, and Besredka is of the opinion that it "explains why in France serum accidents have always been relatively rare, and why in the small number of cases (13 per cent) in which they occur they are not of such a serious nature as they are in countries where sera are not heated."

Cases Requiring Desensitization. — Not all persons who have received injections of normal or immune horse serum become sensitized or require desensitization before subsequent injection may be given.

In the majority of instances serum is given subcutaneously or intramuscularly for the prophylaxis and treatment of diphtheria or the prophylaxis of tetanus, and while serum sickness may follow, desen-

[1] Anaphylaxis and Antianaphylaxis, translated by Gloyne, St. Louis, C. V. Mosby Company, 1919.

PLATE XXVII

Local Serum Anaphylactic Reactions.

Dr. W. P.: Anaphylactic reactions fifteen minutes after application of serum; rabbit-serum in the upper; horse-serum in the lower. Subject to asthmatic attacks when in an animal house or stable where rabbits, horses, and guinea-pigs are kept. (From Kolmer's Infection, Immunity and Biologic Therapy, W. B. Saunders Company.)

sitization is not absolutely required. *When serum is given intravenously, and especially to individuals who have received serum on a previous occasion or when serum is to be given by any route and even by simple subcutaneous injection to asthmatics or individuals known or suspected to be hypersensitive, desensitization is advisable and necessary.*

Kolmer has formulated the following rules which have proved quite satisfactory in practice for guidance in this perplexing problem:

1. Horse serum should never be given to "horse asthmatics" by any route of parenteral injection—subcutaneous, intramuscular, intrathecal or intravenous—without previous desensitization and very special precautions.

Horse asthma is usually a natural allergy, that is, acquired by unknown means. There are some cases on record, however, where this extreme sensitization has apparently resulted from a previous injection of horse serum.

Some cases of horse asthma yield skin reactions to the proteins of horse hair and dandruff and not to serum, but the majority react to serum as well, and all are extremely bad risks. Desensitization of these persons to the point where an adequate dose of serum may be safely given is a tedious process and frequently impossible by our present methods. Horse serum should be avoided and it is very much desired that our manufacturing laboratories render available diphtheria and tetanus antitoxins and antimeningococcus serum by the immunization of cattle for use in these individuals.

If horse serum is given at all, even after attempts to secure desensitization, the injections should be subcutaneous and the preliminary injection of $\frac{1}{50}$ gr. of atropine is advisable. After the injection the patient should be carefully watched and treated as described on p. 770 if a reaction occurs.

All cases of asthma due to other proteins are risks, and especially if serum is given intravenously and intrathecally (intraspinal injection); likewise cases of thymolymphaticus. At least skin tests should be done and desensitization practised if positive reactions are observed. Subcutaneous injections are the least dangerous if serum must be administered.

2. A skin test should be made before serum is given intravenously, even though it is the first injection of serum the patient has ever received. Even if the reaction is negative it is good practice to give 1 cc. of the serum subcutaneously one hour before the intravenous injection. If the reaction is positive several preliminary subcutaneous injections should be given.

Serum given intravenously is brought into sudden contact with the cells and conditions are perfect for eliciting shock if the cells are sensitized. It is to be remembered, however, that ill-effects may be due to non-specific protein shock, and as these may not be allergic, desensitization may not prevent such symptoms as fever and chills.

The same applies to the administration of serum by intraspinal injection, but the danger is less.

3. When an individual has been injected with horse serum some weeks, months or years previously, and serum is to be administered again by intravenous or intraspinal injection, preliminary desensitization is always advisable regardless whether or not skin tests are made. Skin tests, however, are advisable because if positive reactions are observed desensitization should be more thorough than if they are negative.

4. When serum is to be given by subcutaneous or intramuscular injection, skin tests and desensitization are not necessary if the patient is not asthmatic and if it is the first injection. "Serum disease" may follow five to twelve days after the injection, but is not dangerous.

Occasionally severe allergic reactions of collapse, dyspnea, tachycardia and fall in blood-pressure follow the subcutaneous injection of serum into individuals who have received an injection one to six weeks previously; for this reason a desensitizing injection of 1 cc. of serum one hour previously is advisable before the administration of the balance of the serum by subcutaneous or intramuscular injection.

The following table summarizes this subject in a brief manner:

DESENSITIZATION.

Not required	1. When patient is not asthmatic, has never before received serum, and when the injection is to be subcutaneous, intramuscular or subthecal.
	2. When patient is not asthmatic, but has received serum before, and injection is to be subcutaneous or intramuscular.
Advisable	1. When serum is to be given for the first time intravenously to an individual who has not received an injection of serum on a previous occasion.
	2. When serum is to be given intravenously or intrathecally to an individual who has received serum on a previous occasion.
	3. When serum is to be given subcutaneously, intrathecally or intravenously to an individual who is an asthmatic and regardless of whether or not serum has been previously administered.

Methods for Specific Desensitization.—Unfortunately, methods proving satisfactory for the desensitization of guinea-pigs and other of the lower animals do not desensitize human beings equally well. Ordinarily four methods may be employed according to circumstances, as follows:

(*a*) **Precautionary Desensitization: Individual Not Asthmatic and Skin Test Negative.**—Sterile horse serum (either normal serum or the immune serum to be employed) should be injected subcutaneously in dose of 1 cc. at least one hour and preferably two hours, before the balance of serum is administered. If the serum is to be given intravenously, the first few cubic centimeters should be injected very slowly. Desensitization persists for from six to eight hours to several days.

The following methods are modified after those of Besredka when

serum is to be injected subthecally: *Method A:* Give 2 cc. by intraspinal injection and balance (20 to 30 cc.) one or two hours later. *Method B:* Dilute 2 cc. serum with 18 cc. of sterile saline solution in a 20-cc. syringe and give 1 cc. (=0.1 cc. undiluted serum) intraspinally; while the needle is still in the vein wait three minutes, and if there are no symptoms inject the balance of 14 cc. Serum may now be given subthecally at any stage of the illness.

(*b*) **Required Desensitization: Individual Not Asthmatic, but Skin Test is Positive and Serum is to be Given Subcutaneously or Intramuscularly.**—Usually the above subcutaneous method is sufficient or the following: Subcutaneous injection of 0.5 cc. serum followed in one hour by 1 cc. Two hours later the balance of serum by subcutaneous or intramuscular injection.

(*c*) **Required Desensitization When the Individual is Not Asthmatic, but the Skin Test is Positive and Serum is to be Given Intravenously or Intrathecally.**—In these cases desensitization is tedious and time-consuming inasmuch as it should be more thorough; the following method is employed in the Rockefeller Hospital:[1] subcutaneous injections of 0.025 cc. serum followed at one-half-hour intervals by 0.05, 0.1, 0.2 0.4 and 1 cc. If a mild reaction follows the injections may be continued by intravenous injections at one-half-hour intervals beginning with 0.1 cc. and doubling the dose at each injection. If a general reaction occurs, as cyanosis, dyspnea or increased rapidity of the heart-rate supervenes, the injections should be suspended for two to four hours, depending upon the severity of the reaction, and then be resumed, starting with the same dose as that producing the reaction. After 25 cc. of serum have been given in these small doses, after a lapse of four hours, 50 cc. may be given, followed by the regular dose six to eight hours later. Fortunately, one rarely is called upon to employ this measure; at the Rockefeller Hospital it has been found necessary to desensitize in this way only 2 or 3 patients in a series of 150 cases.

In addition to these attempts at specific desensitization, medicinal means may be employed for the prevention of shock as described below.

(*d*) **Required Desensitization when the Individual is a Horse Asthmatic.**—The administration of serum by any route of injection is dangerous, and, if possible, should be avoided. This is particularly true if skin tests with serum are positive; if skin tests with serum are negative the danger is less, *but by no means absent.* Fortunately, these cases are uncommon. But if serum is absolutely required for therapeutic purposes the injections should always be subcutaneous and started with 0.001 cc. or less, followed at one-half-hour intervals by gradually increasing amounts. Atropine sulphate and adrenalin may be administered in addition as precautionary measures, the method being described in the following section.

[1] Monograph No. 7 on Acute Lobar Pneumonia, 1917.

Medicinal Prophylaxis of Anaphylactic Serum Shock.—Two drugs have been found useful in the prevention of anaphylactic serum shock of guinea-pigs, namely, atropine sulphate and adrenalin chloride.

As first shown by Auer,[1] and confirmed by Anderson and Schultz,[2] Karsner and Nutt,[3] atropine prevents or relieves the active bronchoconstriction induced by serum anaphylaxis; similar effects were observed by Bredl and Kraus,[4] with peptone, and by Baehr and Pick,[5] with both peptone and histamine. Friedberger and Mita[6] were unable to demonstrate any appreciable effects of atropine upon serum anaphylaxis. However, Hanzlik and Karsner[7] have again confirmed earlier work and found that atropine in guinea-pigs, in the dosage of 0.01 mg. per gram of body weight, can completely prevent the toxic effects produced by the intravenous injection of beef serum and peptone.

The effects of adrenalin are more complicated and not so certain, depending in part on the functional state of the bronchiolar musculature and in part on the time of administraion, since the action is of short duration. Hanzlik and Karsner found that adrenalin in dosage of 0.0005 cc. of 1 to 10,000 per gram of body weight intravenously prevents death from true anaphylactic shock in guinea-pigs. Pelz and Jackson[8] also found adrenalin to relax the constricted bronchi in anaphylactic shock if injected early.

In the prophylaxis of serum anaphylactic shock of man atropine sulphate in dose of $\frac{1}{50}$ gr. may be given an adult by subcutaneous injection about one-half hour before the serum is administered. Adrenalin chloride in dose of 1 cc. of a 1 to 1000 dilution should be in readiness for injection if necessary.

Sodium chloride has been found by Langer,[9] Brodin, Richet, and Girons[10] as a prophylactic for anaphylaxis in the lower animals, the latter administering 0.8 gm. per kilogram of body weight to dogs.

According to Besredka *ether* narcosis reduces the tendency to anaphylactic shock. Under very exceptional circumstances it may be advisable to reduce the chances of anaphylactic shock in human beings by light etherization.

TREATMENT OF SERUM ANAPHYLAXIS.

For the immediate reaction sometimes developing within fifteen minutes after the administration of serum, and especially by intravenous and intrathecal injection, *adrenalin chloride* (1 to 1000) should

[1] Am. Jour. Physiol., 1910, **26**, 439.
[2] Proc. Soc. Exper. Biol. and Med., 1910, **7**, 32.
[3] Jour. Am. Med. Assn., 1911, **47**, 1023.
[4] Zentralbl. f. Physiol., 1910, **24**, 258.
[5] Arch. f. exp. Path. u. Pharm., 1913, **64**, 65.
[6] Ztschr. f. Immunitäts., 1911, **11**, 501.
[7] Jour. Pharm. and Exper. Therap., 1920, **14**, 425.
[8] Ibid., 1918, **11**, 173.
[9] München. med. Wchnschr., 1912, **59**, 2545.
[10] Rev. d. méd., Paris, 1920, **37**, 7.

be injected intramuscularly in dose of 1 cc. (ℳxvj). *Atropine sulphate* should also be injected subcutaneously in dose of 0.5 mg. ($\frac{1}{120}$ gr.) *Whenever serum is given intravenously it is a good routine practice to have these two medicaments ready in syringes for immediate use;* usually they are not required, but if needed, no time should be lost in the administrations. If the pulse is particularly soft and rapid strophanthin may be given intramuscularly in dose of 0.5 mg. ($\frac{1}{120}$ gr.) or an equivalent preparation of digitalis.

In the usual case of serum sickness the urticarial rash is the most distressing symptom. A brisk cathartic should be given. Ephredrine hydrochloride in dose of $\frac{1}{2}$ gr. for children in capsules every four hours sometimes affords prompt relief; the dose for adults may be 1 gr. If this fails the subcutaneous injection of adrenalin chloride, 1 to 1000, in dose of 0.5 to 1 cc. (ℳvij to xvj) often affords instant relief which may persist for several hours. In severe cases we usually give an injection late in the evening in order that the patient may have a few hours of sleep. Calcium chloride and lactate, in doses of from 3 to 5 gr., have been advocated as a prophylactic and cure, but they are of doubtful utility. Sometimes the administration of a sedative dose of morphine sulphate is indicated along with an injection of adrenalin. A soothing lotion should be applied to the skin, the following well-known calamine lotion being efficacious:

Phenol	2 cc.
Calamine	4 gm.
Zinc oxide	8 gm.
Glycerol	12 cc.
Lime water	16 cc.
Water up to	120 cc.—M.

Aspirin may be administered for headache, myalgia and neuritis. Aspirin or sodium salicylate combined with sodium bicarbonate may be given every four to six hours for the joint pains.

CHAPTER XVIII.

VINCENT'S ANGINA.

It would appear that a variety of ulcerative and suppurative lesions in different parts of the body may be caused by a spirochete in association with a fusiform-shaped bacillus. When occurring on the tonsils, uvula and neighboring parts the disease is known as *Vincent's angina,* and not infrequently mistaken for diphtheria or for those anginas caused by streptococci, pneumococci and staphylococci.

The disease may also occur elsewhere in the mouth and especially on the mucosa of the cheeks and gums, and infection of the latter is sometimes designated as *trench mouth* or *spiro-fusillar gingivitis.* From the mouth it may spread to the nose and the nasal accessory sinuses, especially the antra of Highmore. It may also extend to the middle ear by way of the Eustachian tubes and even to the orbits.

Apparently the infection may also extend downward into the trachea and bronchi and produce a type of spirochetic bronchitis and gangrene of the lung commonly designated as *pulmonary spirochetosis.* Abscesses of the brain, liver and elsewhere have been apparently caused by the fusiform bacillus as likewise a type of ulcerative balanitis known as the "fourth venereal disease" by the spirochete and bacillus.

The organisms have been found in the saliva of normal mouths and are frequently found in traumatic, cancerous, syphilitic and tuberculous ulcers of the tongue, lips, gums, cheeks and throat where they may produce a superficial secondary infection. They appear to have a special predilection for lymphoid tissues.

In other words, the organisms described by Plaut and Vincent are apparently widely distributed and especially in the mouths of human beings. Under conditions not well understood at present they are capable of producing an ulcero-membranous angina constituting typical Vincent's angina. They may also cause a gingivitis designated erroneously as Vincent's angina but also known as trench mouth and spiro-fusillar gingivitis. They may also cause a stomatitis designated as Vincent's angina of the cheeks, lips and tongue. And as stated above, they may apparently infect the bronchi, lungs and other portions of the body.

It would appear, therefore, that the better name for the infection as a whole is *spiro-fusillar disease or Vincent's infection,* reserving the phrase "Vincent's angina" for infection of the throat. Thus we may have Vincent's infection of the gums, cheeks, nose, ear, bronchi, lungs and other parts of the body, but it is obviously a mistake to speak of these as "anginas."

Definition.—Vincent's angina may be defined as a specific infectious ulcero-membranous disease of the throat caused by Spirochæta vincenti and Bacillus fusiformis.

It does not properly include infections of the gums, buccal mucosa and neighboring tissues with these organisms, but since the lesions of the oral and nasal cavities caused by the same organisms are commonly designated as "Vincent's angina" we are including them in this chapter.

Synonyms.—The *angina* is also known as *Plaut-Vincent's angina, diphtheroid angina, ulcero-membranous angina,* etc. The *infection* in other parts of the mouth is also known as *trench mouth* or *spiro-fusillar gingivitis, spiro-fusillar stomatitis,* etc.

FIG. 151.—The spirochetes and fusiform bacilli of Vincent's angina.

THE ETIOLOGY OF VINCENT'S ANGINA.

In 1894 Plaut[1] incidentally mentioned the occurrence of spirochetes in association with the "bacillus of Miller" in certain "diphtheroid" anginas, but the disease as an entity was first clearly established by Vincent[2] in 1904.

Two organisms are found in smears of the lesions, namely, a spirochete and a large slightly curved pointed bacillus. The former is designated Spirochæta vincenti and the latter Bacillus fusiformis (Fig. 151).

[1] Deutsch. med. Wchnschr., 1894, **20**, 920.

[2] Bull. et mém. Soc. méd. d. hôp., 1904, **21**, 1111; Lancet, 1905, i, 1260; Ann. d. l'Inst. Pasteur, 1896, **12**, 488; La Semaine méd., 1898, **18**, 109.

Both organisms are anaërobic and cannot be cultivated by ordinary methods. Bacteriological diagnosis is made by the examination of smears and not by cultures.

Whether or not Spirochæta vincenti is a separate and distinct organism or one of the spirochetes commonly found in the mouth, cannot be stated. It may be a distinct entity, or what is called Spirochæta vincenti may be one of the saphrophytic mouth spirochetes capable of assuming a pathogenic role in lesions caused by the fusiform bacillus.

Pratt[1] states that fusiform bacilli have been found in the mouths of 100 per cent of human beings. If this is true it must be assumed that some other factor predisposes to infection by them or in some way favors an increase of virulence; or it may be that the spirochete initiates infection followed by secondary infection with fusiform bacilli. Different serological types of the latter have been described by Varney,[2] and while long, wavy forms have been seen in cultures somewhat resembling spirochetes it is now certain that the two organisms are separate and distinct. Undoubtedly fragments of Leptothrix buccalis and similar organisms are sometimes mistaken for fusiform bacilli and especially in smears of secretions from the gums and ulcers of the cheeks. The typical bacilli are found in typical Vincent's angina of the fauces.

All forms of Vincent's disease are infectious, but the angina and gingival forms are especially apt to spread among individuals in close contact. It is more common in winter, probably because of contact in schools and theatres, where large audiences are crowded in small and badly ventilated halls or rooms. The disease appears to be increasing in frequency. It may be disseminated by kissing, eating utensils and by "droplet" infection in sneezing and coughing.

It is probable that constitutional factors, and especially faulty food and vitamin deficiency, achylia, diabetes, etc., predispose to the disease and especially the gingival infections. In the gingival lesions of the leukemias and aplastic anemias, Vincent's infection is commonly observed, and the agranulocytic angina recently recorded by Lovett[3] was probably an infection of this kind. Neglect of oral hygiene is unquestionably a predisposing factor as likewise all states of subnormal health and vitality.

The organisms are especially likely to be found in the crevices about the teeth. Gingival infections are not found in mouths from which all the teeth have been extracted, nor have we seen the true angina of the throat under these conditions. Indeed the disease is quite uncommon when the teeth are kept smooth and clean and when pyorrhea and recession of the gums are absent.

All *ages* are susceptible, but true Vincent's angina is most common

[1] Jour. Infect. Dis., 1927, **41**, 461.
[2] Jour. Bacteriol., 1927, **13**, 275.
[3] Jour. Am. Med. Assn., 1924, **83**, 1498.

among children and adolescents. Gingival and oral infections are more common among adults, but institutional children may also show a large percentage of spongy bleeding gums due to this infection.

Sex does not appear to have any definite influence, although in our experience men are more apt to show gingival infections than women, probably because they are not as careful as the latter in matters of oral hygiene.

Race has some influence in that the colored are less apt to develop the oral lesions than are whites. The disease is very uncommon among dogs and other of the lower animals.

IMMUNITY TO VINCENT'S ANGINA.

One attack of Vincent's angina does not appear to give protection against subsequent attacks. Unquestionably spontaneous recovery from the angina usually occurs, but this is probably due more to phagocytosis and the local destruction of the organisms than to antibody production. Gingival and oral lesions may also recover spontaneously, but the former are apt to run a prolonged chronic course with acute exacerbations. As is true in syphilis and other spirochetic diseases antibodies may be produced sufficient for holding the infection latent for varying periods of time, but immunity does not appear to develop to as high degree as in many of the bacterial infections.

One of us has used saline solution suspensions of the exudate as antigen in complement-fixation tests employing the sera of infected individuals up to the sixteenth day of the disease, but with uniformly negative reactions; negative reactions were also observed in a series of chronic gingival infections. It may be that the spirochetic infection may produce antibody responsible for temporarily positive Wassermann reactions, but none have been observed in our experience with the new Kolmer method.

THE SYMPTOMATOLOGY OF VINCENT'S ANGINA.

In typical Vincent's angina the majority of patients do not appear very sick, and one is often surprised to note the extensive exudate and comparative absence of toxemia and pain. The exudate is usually dirty yellow in color, sometimes brown, due to the presence of decomposed blood; it crumbles somewhat when touched with a probe and bleeds easily. There is usually well-marked ulceration and sloughing; the uvula often seems to melt away. The breath is foul; the odor is somewhat characteristic and quickly permeates the room or ward. One often suspects the presence of the disease from the odor alone. In the second group of cases the condition may be easily overlooked. The gums are involved and attention may be attracted to the condition because the gums bleed easily when the child coughs or bites into a piece of bread. Inspection shows the infected tissues to be

spongy, especially along the margin, and easily separated from the teeth. Soon the inevitable punched-out ulceration appears with a thin, filmy exudate. The teeth may loosen, and in a few cases the ulceration extends to quite a depth with destruction of the soft parts. One of us had the opportunity of observing a case of this kind in an institution for children. Destruction was so extensive as to infect the left antrum of Highmore. There was extensive edema of the overlying tissues and well-marked exophthalmos and edema of the capsule of Tenon. The organisms were found in great abundance in the primary lesion, and in the nasal discharge and after death, in the antrum.

Bloodgood[1] has described the oral lesions as follows: "The mucous membrane lining the three communicating chambers—oral cavity, fauces and pharynx—may be diffusely involved, or there may be only a single spot of a few millimeters in diameter. The single spot is the unit, and the diffuse lesion is only a multiplicity of single spots. The single spot is at first a red area of irregular outline, never sharply defined, of such a peculiar redness that it might be called the erysipelas of the mouth. The center of the red area may be covered with a whitish or grayish patch which is really due to the superficial destruction or necrosis of the red mucous membrane. Beyond this superficial slough there is still a red zone. It is not unlike a minute gumma in which a central zone of necrosis, surrounded by the red zone of collateral anastomoses of increased vascularity, is recognized. In this stage, because of the little gray or whitish slough, the condition may be confused with leukoplakia, but the latter is never surrounded by an inflamed and reddened mucous membrane. Leukoplakia and Vincent's angina may appear together. In the next stage the slough comes away and leaves an ulcer. Thus there may be, in this infection called Vincent's angina, single or multiple red areas, single or multiple areas covered with a superficial slough, or single or multiple ulcers. Now and then one or more of the ulcers may be quite large, although rarely more than 18 mm. in diameter; usually the single unit areas are only a few millimeters in diameter. The ulcer never looks like a mucous patch, and it never has the ragged excavated edge of the tuberculous ulcer or the induration of the cancerous ulcer."

Vincent's infection may assume serious proportions and cause much harm. Important vessels may become eroded, and hemorrhage may follow. The stomatitis may cause loss of a greater or less amount of tissue. As a result of this injury, the vitality of the teeth may become subsequently impaired. Osteomyelitis may occur as a complication. Reasoner and Gill[2] have seen one such infection in which an extensive, bilateral osteomyelitis of the inferior maxilla followed a Vincent's gingivitis subsequent to the extraction of a tooth. It resulted in the destruction of the bone, with the exception of the epiphyses. Both the spirochete and the fusiform bacillus were recovered from the cortex

[1] Jour. Am. Med. Assn., 1927, 88, 1142.
[2] Ibid., 716.

of the medulla of the infected bone. Enlargement of cervical and mediastinal lymph nodes is a sequel which may assume serious proportions, and bronchial spirochetosis is a grave malady, sometimes terminating fatally. A fatal case of mastoiditis has been described by Ottoni[1] in which Spirochæta vincenti was the causative agent. Emerson[2] reported 915 Vincent's infections in the American Forces in France, with 1 death. This number was, of course, only a small part of those which actually occurred.

THE DIAGNOSIS OF VINCENT'S ANGINA.

The diagnosis of Vincent's infection is made with certainty only by bacteriological examination. The angina may be clinically mistaken for diphtheria even by the most expert.

Bacteriological diagnosis requires nothing more than the examination of simple smears on slides or cover-slips. *Cultures are of no use,* although smears may be made from the swabs used for making cultures for diphtheria providing that they have not become dried; in this way both examinations are possible from the same swabs. One of us has occasionally found spirochetes in smears of cultures on Loeffler's medium for diphtheria bacilli, being mechanically deposited on the surface of the medium and recovered next day in stained smears, which have led to a suspicion of Vincent's infection subsequently verified by the examination of direct smears.

The spirochete of Vincent is a motile, somewhat irregular, spiral body or spirochete from 10 to 30 microns in length and about 0.5 micron in thickness. The fusiform bacillus is spindle-shaped, from which it takes its name. It is thickest at the center and the extremities taper irregularly to a point. It exhibits distinct staining reactions with most of the ordinary stains. Portions of the protoplasm stain more deeply than others and give a barred appearance to the stained bacterium. Miss Clara Kast, of the Research Institute of Cutaneous Medicine, has found cultures non-motile.

Tunnicliff[3] has demonstrated that the spirochetes precede the fusiform bacilli in invasion of the tissues, and on this basis has separated the local pathological area into three zones: The innermost or deepest of these is rich in spirochetes; the intermediate zone contains spirochetes and fusiform bacilli, and in the outermost, which is the necrotic membrane, most organisms are found together with other bacteria. This observation gives weight to the contention that the spirochete is responsible for the production and spread of the disease.

The bacilli are easily stained by the anilin dyes, especially gentian violet. They are generally negative to Gram's stain if decolorization is thorough. The spirilla stain with more difficulty and are Gram-

[1] Jour. Am. Med. Assn., 1920, **74**, 1474.
[2] Mil. Surg., 1921, **49**, 642.
[3] Jour. Infect. Dis., 1919, **25**, 132.

negative. We secure good preparation by staining according to the method of Gram, with incomplete decolorization and counterstaining with undiluted Ziehl-Neelson's carbol fuchsin. The bacilli are stained a dark violet-brown and the spirilla a deep pink.

Both organisms may be recognized in wet preparations even without dark-field examination. All dentists should be able to make the simple examinations required; the technique is readily learned. At any rate, smears are easily made and satisfactorily examined in any qualified laboratory.

THE TREATMENT OF VINCENT'S ANGINA.

Local measures are ordinarily sufficient. Bloodgood has highly recommended applications of a thick paste of chemically pure sodium perborate in water. This should be applied to the gums or other lesions with a swab and allowed to remain for at least five minutes. During this time it foams as a result of oxidation. The mouth is then rinsed out with warm water.

For more extensive lesions a gargle of a thinner solution may be used. In the Evans Institute and School of Dentistry of the University of Pennsylvania a mouth wash is made up as follows by the patient:

A scant $\frac{1}{4}$-teaspoonful of salt.
A scant $\frac{1}{4}$-teaspoonful of powdered borax.
A teaspoonful of hydrogen peroxide.
A large glass of *hot* water (120° to 125° F.).

The solution is made *fresh* when needed and used as a mouth wash and gargle three or four times a day. The entire quantity should be used up, holding suitable portions in the mouth for about one-half minute.

For the gums the local application of 2 to 7 per cent solutions of chromic acid are sometimes efficacious. Dr. Prinz, of the Evans Institute, prefers 8 per cent solutions of zinc chloride applied to the gums or sores with a swab. About twenty minutes later a second application is made followed by an application of balsam of Peru. This treatment is repeated next day and sometimes suffices for bringing about a cure.

Solutions of potassium chlorate, copper sulphate, iodine, mercurochrome, methylene-blue and acriflavine have been recommended; also Dakin's solution and solutions of arsphenamine and neoarsphenamine. The latter are particularly efficacious and may be prepared as follows:

Arsphenamine	0.4 gm.
Hot water	10.0 cc.
Dissolve and add	
Glycerin	10.0 cc.

This gives a 2 per cent solution in 50 per cent glycerin which is frequently applied with swabs. Or 0.9 gm. of neoarsphenamine may

be dissolved in 15 cc. of water and applied in the same manner. Or pastes of either may be made in water or glycerin and applied.

In severe cases of Vincent's angina neoarsphenamine may be injected intravenously or sulpharsphenamine intramuscularly, the doses for adults being 0.9 and 0.4 gm. respectively, children receiving less in proportion to body weight. Two to four injections at intervals of four or five days may be required to check the disease. If these fail it may be well to try tartar emetic by intravenous injection in dose of 5 to 10 cc. of a sterile 1 per cent solution as recommended by Driscoll. Intramuscular injections of bismuth have also been recommended.

PROPHYLAXIS IN VINCENT'S ANGINA.

Patients with typical Vincent's angina should be isolated until all clinical evidences of the disease have disappeared and smears found negative for the organisms. In the gingival and oral varieties the infectious nature of the disease and the possibility of transmission by kissing, sneezing and coughing should be explained to the patient as likewise the possibility of infection from tooth-brushes, drinking cups and eating utensils. Dentists should be particularly careful in the sterilization of all instruments employed in making local applications, and it might be a good plan for them to wear rubber gloves.

As shown by Reasoner and Gill soaps have definite spirochetical properties and patients should be advised to carefully brush their teeth and gums at least twice a day. In addition one of us[1] has employed the following special tooth paste:

Mercurophen or metaphen	0.5 gm.
Tooth paste	100.0 gm.

Tooth paste of this kind can be made agreeable to patients and we believe should be prescribed for all cases during active treatment and as a routine prophylactic against reinfection. They are well borne by the gums and need not be feared from the standpoint of systemic poisoning from swallowing small amounts during application, although patients should be informed of their nature and cautioned against swallowing the paste. Both mercurophen and metaphen are slightly less toxic than mercuric chloride, but even were they of the same toxicity, the swallowing of 1 gr. a day would not produce toxic effects, and this would correspond to about 10 gm. of the paste. It is likely that smaller amounts of mercurophen or metaphen could be used, like 0.1 to 100 gm. of paste giving a 1 to 1000 dilution, but the bactericidal and spirocheticidal effects are less. It is our custom at present to prescribe 0.5 gm. per 100 gm. of paste during the active treatment of the disease and to reduce the amount down to 0.1 to 0.2 gm. per 100 gm. for routine prophylactic use.

In using these pastes it is well to show the patient how to rub small

[1] Kolmer: Jour. Am. Dent. Assn., 1925, **12**, 381.

amounts into the gums by means of the index finger; the paste is left for at least a minute or two when brushing is done in the usual manner with a brush softened in warm water. As a general rule, sufficient saliva is present to give a good lather.

In addition it is sometimes advisable to prescribe a lotion for use several times a day and the following can be recommended:

Mercurophen	0.1 gm.
Peppermint water	100.0 cc.

This gives a 1 to 1000 solution of mercurophen, and bactericidal tests have shown that it is capable *in vitro* of completely sterilizing in one minute an equal part of undiluted saliva in final dilution higher than 1 to 200,000 or an equal part of a 1 to 100 dilution of a twenty-four-hour broth culture of staphylococci in final dilutions as high or higher than 1 to 200,000. About a teaspoonful of solution may be diluted with 2 or 3 parts of water, taken into the mouth and left in contact with the gums for several minutes, when it should be expectorated and the mouth rinsed with water if the taste is disagreeable. Mercurophen does not form amalgams with metallic fillings of teeth.

CHAPTER XIX.

MUMPS.

Definition.—An acute specific infectious disease, characterized by swelling of the salivary glands, especially the parotids, and a special tendency to orchitis in males.

Synonyms.—*Parotitis epidemica; specific parotitis; "mompen;" "the branks."* French, *Oreillons.* German, *Siegenpeter.* The swelling of the glands, difficulty in opening the jaws and the tendency to mumbling speech probably accounts for the popular term of *mumps.* Moreover the disease can occur without involvement of the parotid glands, so that the name of "mumps" has a better claim to usage than that of epidemic parotitis.

History.—Undoubtedly the disease and its peculiarities was known to Hippocrates, who described in his book of *Epidemics* its occurrence in children and young adults, the absence of suppuration and its most common and dreaded complication, orchitis. Hamilton (1761), of Scotland, and Mangor (1773), of Germany, however, appear to have first recognized it as an acute infectious disease and to have differentiated it from other diseases involving the face and neck, like tonsillitis, diphtheria and stomatitis.

THE ETIOLOGY OF MUMPS.

Mumps has a universal distribution. It has occurred in every country of the world and is especially prone to become epidemic where large numbers of boys and young men are congregated together as in schools and camps. Curiously it does not usually spread rapidly and widely, as may scarlet fever and measles, but tends to be restricted to a particular school or locality.

Though occurring at all times of the year, the *seasonal incidence* for most epidemics is the spring and autumn; epidemics rarely occur during the summer months.

Sex does not appear to exert any influence, although on account of the frequency of orchitis it is a common impression that mumps occurs more frequently in males.

No *age* is exempt, although the majority of cases occur between the years of five and fifteen; it is uncommon below two years and persons above puberty are less liable to infection. Young adults are commonly infected in epidemics in schools and camps, but the disease is rare after middle life; fatigue, overcrowding and poor hygienic surroundings may act as predisposing factors by lowering resistance.

Cases have been reported in which children have been born with mumps during the terminal stages of pregnancy in women with the disease.

Bacteriology of Mumps.—While the disease is undoubtedly infectious the virus has never been isolated or identified. It is now practically certain that the diplococci found by Laveran and Catrin,[1] in 1893, Mecray and Walch,[2] in 1896, Michaelis and Bienn,[3] in 1897, Busquet and Feri,[4] in 1896, Teissier and Esmein,[5] in 1906, and by Herb,[6] in 1909, in cultures of saliva, aspirated parotid glands, Steno's duct, swollen testicles, the blood, etc., of individuals with the disease were contaminating organisms and especially staphylococci capable of exciting inflammatory changes when injected into the lower animals. Kermorgan[7] has recently described a spirochete as the etiological agent, but this claim lacks confirmation.

It is practically certain, however, that the virus is present in the fluid aspirated from the parotid glands and likewise in the saliva and blood during the acute stages of the disease.

Granata[8] was the first to conclude that the virus may be filterable, basing his conclusions upon the results obtained by inoculating the sterile saliva filtrates from two patients into the blood, parotid glands and subcutaneous tissues of rabbits.

Gordon[9] also produced a meningeal type of the disease in monkeys by intracerebral injections of sterile filtrates of saliva; one animal injected intraperitoneally and intravenously became ill on the eleventh day and showed swelling of the parotids and stiffness of both jaws, but without nervous symptoms and with complete recovery. Attempts to transfer the "disease" from one monkey to another with filtrates of the brain and cord from fatal cases proved entirely unsuccessful.

Nicolle and Conseil[10] at the same time and independently showed that the injection into the parotid glands of monkeys of sterile fluid aspirated from the glands of patients with mumps, produced a brief febrile reaction after an incubation period of sixteen to twenty-six days. One animal also developed a definite swelling of the left parotid gland, while another showed a lymphocytosis of the blood which is commonly noted in cases of the disease.

Wollstein[11] has shown that cats injected into the parotid gland and testicle with the bacterial sterile filtrate of the salivary secretion of children in the active stage of mumps can be made to develop a pathological condition having several points of resemblance to that present in the disease in human beings. Her work has shown in an especially convincing manner that the saliva contains a filterable and

[1] Compt. rend. Soc. d. biol., 1893, **5**, 528.
[2] Med. Rec., 1896, **1**, 440.
[3] Verhandl. Congr. f. inn. Med., 1897, **15**, 441.
[4] Rev. d. méd., 1896, **16**, 744.
[5] Compt. rend. Soc. d. biol., 1906, **50**, 803, 853.
[6] Arch. Int. Med., 1909, **4**, 201.
[7] Compt. rend. Soc. de biol., 1925, **92**, 1370; Ann. d. méd., 1926, **19**, 301.
[8] Med. ital., 1908, **6**, 647, 672.
[9] Reports to the Local Government Board on Public Health and Medical Subjects, London, 1914, No. 96; Lancet, 1913, ii, 275.
[10] Compt. rend. Acad. d. sci., 1913, **147**, 340.
[11] Jour. Exper. Med., 1916, **23**, 353; 1918, **28**, 377.

infective agent. It was detected most readily in the saliva during the first three days of the disease, less easily on the sixth day and not at all on the ninth day. It was detected also in the blood of patients showing marked constitutional symptoms, and in the saliva of a case of recurrent mumps at the periods of enlargement of the parotid glands, but not two weeks after the swelling had subsided. It was not detected in the cerebrospinal fluid.

Ritossa and Nastasi[1] report that all rabbits inoculated with blood or puncture fluids from the parotid glands of patients with mumps, died in three to five days; some of the animals are stated to have shown hyperemia and infiltration of the testes and parotid glands.

Infection and Dissemination.—These experiments show, therefore, that the virus lies in the buccal and nasal cavities of the patients, and the disease is doubtless transmitted by "droplet" infection in sneezing, coughing, etc. The virus is killed at 55° C. and probably dies quickly upon exposure and drying; at least it does not appear to be readily spread or carried by third persons, but rather by direct contact. Nurses do not ordinarily carry the disease from patient to patient in separate rooms, but in a hospital ward the disease may spread rapidly, the patients in adjourning beds being first to be affected.

An individual exposed to the disease does not appear to transmit the virus to others until about four days before the onset of symptoms, and since the incubation period is usually twelve to twenty-four days it would appear safe to allow a child to attend school for the first week after exposure.

The disease is most infectious during its height and the danger is present as long as any swelling of the parotid glands and testicles is apparent.

Quarantine.—The period of *isolation* is ordinarily three weeks. This is especially important in the cases of males over fourteen years of age since the onset of orchitis is occasionally late. Isolation should be continued in all orchitis cases until the complete disappearance of acute swelling. In women and in children of both sexes it is a safe rule to maintain quarantine for at least one week after the complete disappearance of all swelling and symptoms, but since complications are less likely among them, the whole period of isolation may be reduced to two weeks in mild cases by this rule.

The virus appears to be short lived, and terminal *disinfection* does not appear to be very important, but this is advisable in hospitals and other institutions.

IMMUNITY TO MUMPS.

The majority of human beings are apparently susceptible, although not a few escape even when exposed and pass through life without contracting the disease. This is probably due, however, more to

[1] Pediatria, 1926, **34**, 825.

fortunate escape from infection than to natural immunity, since almost direct contact with the disease is necessary for infection.

The lower animals are believed to be immune, although dogs may suffer with a form of parotitis resembling the disease in human beings.

One attack usually confers immunity for life. Second and even third attacks are said to occur but it is exceedingly difficult to prove these authentic cases of second infection.

Cramen[1] has recently described a case of mumps localized exclusively in the sublingual glands occurring in a boy, aged sixteen years, who had had mumps three years before with involvement of the parotid and submaxillary glands and testicles which was believed to have left these glands locally immune.

Following recovery antibodies are apparently present in the blood capable of affording protection for the balance of life. On this basis injections of convalescent blood and serum have also been advocated for the prophylaxis of the disease as discussed below.

PROPHYLAXIS IN MUMPS.

Some writers have expressed the opinion that it is better to allow children to contract the disease before puberty, and to get it safely over than to run the risk of taking it later on in life and of perhaps suffering from atrophy of both testicles and ovaries. But in our opinion this is not justifiable because the orchitis and ovaritis are seldom serious in patients who have been kept in bed, and their risks have probably been overemphasized. Furthermore deliberate exposure may result in contracting the disease and developing atrophic orchitis when with a little care it could be avoided until adult age is reached, when susceptibility is greatly reduced.

In an outbreak in a school, camp or family it is well to take the temperature of all exposed who have never had the disease at least twice a day, and to isolate promptly any contact showing the slightest sign of fever, malaise, headache or earache. Children exposed to the disease may go to school for about a week followed by isolation for two weeks.

Serum Prophylaxis.—Hess[2] has observed that the subcutaneous injection of 6 to 8 cc. of whole blood taken from donors who had had the disease up to one or two years previously, completely protected 20 children in an institutional outbreak. Regan[3] has reported that the subcutaneous injection of 2 to 4 cc. of serum taken from adult donors between the tenth and twentieth days of mumps (usually on the fourteenth to sixteenth days) is capable of affording temporary protection, providing it is given before the seventh day after exposure.

He also suggests that its administration late in the incubation period

[1] Rev. méd. de la Suisse, 1925, **45**, 893.
[2] Am. Jour. Dis. Child., 1915, **10**, 98.
[3] Jour. Am. Med. Assn., 1925, **84**, 279.

may modify the severity of the disease, especially from the standpoint of preventing orchitis, and this is apparently substantiated by the experience of Teissier,[1] who observed 23.29 per cent of orchitis in a series of 174 control cases of mumps treated without serum and but 8.13 per cent in a series of 172 cases injected with 20 to 40 cc. of convalescent serum. Teissier[2] also reports that but 1 of 22 girls, from six to eighteen years of age, injected with 10 to 20 cc. of serum contracted the disease in an institutional outbreak. De Lavergne and Florentin[3] also state that the subcutaneous injection of 20 cc. of convalescent serum appears to afford protection against the development of orchitis, and we will refer to this subject again under the treatment of the disease.

PERIOD OF INCUBATION OF MUMPS.

When a child with mumps is admitted into a hospital ward the contacts usually develop the disease fourteen to twenty-one days later, and this may be accepted as the usual period of incubation.

But it is subject to considerable variation, being shorter in epidemics probably by reason of enhanced virulence of the virus; or it may be a few days longer, so that in general terms the period of incubation in the great majority of cases falls within twelve to twenty-four days after exposure.

THE SYMPTOMATOLOGY OF MUMPS.

The prodromal symptoms for the first day or two usually consist of a mild fever (99° to 100° F.), loss of appetite, malaise, dryness of the throat and bodily aches and pains. In exceptional cases and especially in adults the disease may be ushered in with chills, fever, severe headache and inflammation of the posterior pharyngeal wall. Orchitis may be the first symptom and meningeal symptoms may likewise usher in the disease. In mild cases in children there may be no fever at all.

These are followed by sudden pain or stiffness at the angle of the jaw, headache and higher temperature. Soon the right or left parotid gland shows a soft and rather diffuse swelling filling up the hollow between the ear and the angle of the jaw. The skin is generally not red, although sometimes tense and shiny, nor is there any marked tenderness on palpation, save in cases of extreme swelling; fluctuation never occurs. In extreme cases the slightest touch causes exquisite pain with difficult and painful swelling reaching to the clavicles. Occasionally there is edema in the upper part of the face, chiefly about the eyelids. The neighboring lymphatic glands may be slightly

[1] Bull. méd., 1925, **39**, 349.
[2] Bull. d. l'Acad. d. méd., 1925, **93**, 369.
[3] Paris méd., 1925, **55**, 522; Bull. d. l'Acad. d. méd., 1925, **93**, 362.

enlarged and tender. Earache may occur and is sometimes severe. The submaxillary gland may be swollen and tender. Occasionally a slight trismus is present with clenched teeth, as if from some reflex action.

It is exceptional for both parotids to be involved simultaneously. Usually the second gland becomes swollen and tender two or three days later and when both glands are swollen the patient's appearance is greatly altered.

The swelling persists for about seven to ten days; by the twelfth day it has usually disappeared. In very exceptional cases the swelling may become chronic and remain for weeks and even months after the general symptoms have subsided. Suppuration is rare. Some thickening and induration of the glands may follow in exceptional cases.

FIG. 152.—Mumps.

Fever is usually present for the first two or three days, but usually falls when the parotid swelling has reached its height.

The buccal mucosa is usually dry and reddened and the orifice of Stenson's duct is commonly acutely congested and appears as a bright red spot at the level of the crown of the second upper molar on the affected side with congestion of the pharyngeal wall. The secretions are scanty and cause some discomfort from dryness of the mouth and throat.

In the vast majority of cases complete recovery occurs within three weeks, with no permanent after-effects. In mild or abortive types

the disease may run its course in a few days and escape diagnosis. But in in some cases, and especially in adolescents and adults, the disease is not as benign and more or less serious complications and sequelæ may occur. During epidemics, and especially in camps when the virus has become highly virulent, the individual may be prostrated from the start, but fortunately this is not of common occurrence. In some instances the parotid glands escape while the submaxillary and lingual glands are involved. Occasionally relapsing cases are seen in which the parotids are first involved followed in succession by involvement of the other salivary glands.

Blood Changes.—Blood changes have been described by a few investigators. Feiling[1] states that a slight leukocytosis occurs with a relative and absolute increase of lymphocytes occurring on the first day of the disease and persisting for at least fourteen days. He believes these changes are of diagnostic value and of aid in differentiating mumps from other inflammatory swellings of the parotid and submaxillary glands.

Bunting and Thewlis[2] state that there is with onset of swelling of the glands a moderate leukopenia followed by a gradual return to normal and then a moderate leukocytosis. Also an early increase of neutrophiles followed by a decrease and an increase of both eosinophiles and lymphocytes, especially the latter. They believe that the virus first affects the neutrophiles with a subsequent response of the lymphoid tissue to toxins produced during the disease.

THE COMPLICATIONS AND SEQUELÆ OF MUMPS.

Orchitis, or rather epididymo-orchitis, is the commonest, most painful and most dreaded complication since the virus appears to have a special predilection for the testicles. Army surgeons have expressed the opinion that the virus may be carried to the penis by the hands and ascend the urethra with infection of the testicles and prostate gland, but the prevailing opinion is that the virus is transported by the blood.

Orchitis is rare in children and uncommon between eleven and fifteen years of age. The fully matured testicles are especially likely to be involved and especially in individuals between sixteen and twenty-four years of age. The incidence varies according to the virulence of the virus and the amount of rest in bed; it is commonly around 6 to 10 per cent, but may reach as high as 20 to 50 per cent, and especially in epidemics among poor surroundings in which the patients do not stay in bed for at least one week.

This complication usually begins five to eight days after the onset of symptoms as the parotid swelling is subsiding; for this reason some authors have spoken of the process as a *metastasis*. In exceptional

[1] Quart. Jour. Med., 1914–1915, **8**, 260. This article also gives an excellent review of the literature on mumps.

[2] Arch. Int. Med., 1926, **1**, 197.

instances the orchitis develops earlier or much later. Involvement is usually ushered in by sudden rise of temperature, restlessness and delirium in severe infections. The testicle or testicles become swollen, red and exquisitely painful with pain along the spermatic cord. The seminal vesicles and prostate gland are sometimes involved and an urethral discharge may occur. Fortunately secondary infection and suppuration are rare.

Atrophy of one or both testicles may occur. This develops slowly and insidiously but may be rapid. The testicle or testicles become small and fibrous, and when bilateral and complete the semen is free of spermatozoa and the individual is sterile, although the libido is usually unaffected. Statistics as to the percentage of cases of orchitis followed by atrophy are lacking, but the number is apparently considerable.

Ovaritis is not nearly as common, as painful or as serious as is orchitis. Atrophy with sterility is rare. Lower abdominal tenderness is usually all that is to be noted. Vulvitis is occasionally seen. *Mastitis* may occur in both sexes and especially girls. *Thyroid enlargement* has been observed.

Acute *pancreatitis* is said to occasionally occur, being first described by Cuche in 1897. More or less abdominal pain with epigastric tenderness may occur during an attack of mumps, generally of sudden onset and sometimes accompanied by severe vomiting. Undoubtedly this is nothing more than acute gastric irritation in most instances, but real pancreatitis is believed to be sometimes responsible; Lemoine and Lepasset[1] have recorded a fatal case with jaundice verified by necropsy.

The virus of mumps also shows at times an effect upon the central and peripheral nervous systems and especially in severe infections of males developing orchitis during epidemics when the virulence of the virus is particularly high.

Meningismus, or so-called "serous meningitis," may occur during the acute state; in rare instances it has developed at the outset. The pressure of the spinal fluid is increased, but otherwise shows no abnormal changes. A true *meningitis*, however, may occur in which the spinal fluid is clear, shows an increased pressure, an increase of total cells due to an increase of small lymphocytes and a slight increase of protein. There is headache, delirium, high fever and sometimes convulsions and vomiting. The symptoms usually subside quickly and the prognosis is good. The *facial nerve* is sometimes involved, owing to its passage through the parotid gland. *Multiple neuritis* has been described. Involvement of the *auditory nerve* with tinnitus and temporary deafness is not uncommon; permanent deafness, however, has occurred. Otorrhea may occur and the labyrinth may be damaged. The deafness, which may be preceded by tinnitus and

[1] Bull. et mém. Soc. méd. d. hôp. d. Paris, 1905, **22**, 640.

vertigo, usually becomes evident within four days of the illness, and has been ascribed by some authors to basal meningitis. *Optic neuritis* may occur, and atrophy has been reported as likewise paralysis of the external muscles of the eye. Irido-cyclitis has been known to both precede and follow the parotid swelling.

Involvement of the *kidneys* may occur. This is usually in the form of cloudy swelling with transient albuminuria, but true nephritis has been described. True *arthritis* is rare, although painful joints are not uncommon during an attack of mumps. The *heart* is rarely involved, although temporary functional disturbances have been reported as likewise rare instances of pericarditis and endocarditis. *Bronchitis* and *bronchopneumonia* have been described.

THE PATHOLOGY OF MUMPS.

The parotid and other salivary glands have shown an acute interstitial inflammation; similar changes have been noted in the experimentally produced disease in monkeys and cats. Sicard and Dopter[1] have found lymphocytes and polymorphonuclear leukocytes in the saliva from Stenson's ducts followed later by desquamated glandular epithelium. The epididymo-orchitis is both parenchymatous and interstitial.

THE DIAGNOSIS OF MUMPS.

Diagnosis is ordinarily an easy matter and especially during epidemics. The position of the swelling in front of and below the ear with elevation of the lobe on the affected side is usually characteristic. In children inflammation of the parotid glands from other causes is exceedingly rare. Adenitis from tonsillitis, diphtheria and scarlet fever can be usually easily differentiated from mumps. In adults septic conditions of the mouth with involvement of the parotid glands, and especially after abdominal operations, may be confusing. It is stated that if vinegar is applied to the tongue a painful reflex secretion of saliva occurs in the affected gland. A differential leukocyte count showing high lymphocytosis is sometimes of aid in diagnosis. The lymphocytosis of the spinal fluid may assist diagnosis and spinal puncture itself is frequently efficacious for detecting (and preventing) malingering among soldiers.

Most difficulty is experienced in cases of primary involvement of other glands, like the submaxillaries, sublingual and lacrimal glands, also cases initiated by orchitis.

THE PROGNOSIS OF MUMPS.

The prognosis is excellent and especially in children. Death is rare and then only in severe complications like meningitis. But even

[1] Compt. rend. Soc. d. biol., 1905, **48**, 317.

with involvement of the meninges the outlook for recovery is very good. Atrophy of the testicles following orchitis is of most importance, but with complete rest in bed and support this danger is greatly reduced.

THE TREATMENT OF MUMPS.

Rest in bed is advisable for all cases during the febrile period, and is particularly important in mumps of males over twelve years of age to lessen the danger of orchitis. In mumps of young men this period of rest should be at least ten days.

A mild purgative is advisable. The diet should be of fluids or semi-solids on account of difficulty of chewing, and care should be taken to see that the patient takes sufficient, as he is sometimes reluctant to eat.

It is important to keep the mouth and throat clean as stomatitis is always present, and a careful toilet may be of service in preventing infection of the middle ear by way of the Eustachian tubes. For this purpose a dessertspoonful of liquor antisepticus in a small glass of warm water may be used as a mouth wash and gargle.

If nasal discharge is present a few drops of 5 per cent argyrol or 10 per cent neosilvol may be instilled into both nostrils several times a day.

All articles soiled with the discharges from the nose and throat should be disinfected. Some physicians are of the opinion that orchitis is produced by transferring the virus to the penis by the hands with ascending urethral infection.

High fever is best controlled by sponge baths.

For bodily aches and pains 5 gm. of acetylsalicylic acid may be given every four hours.

For the swollen glands cold applications may be tried, but children usually prefer hot applications. Gauze wrung out in hot saturated solution of Epsom salts may be laid over the parts with a hot-water bottle or electric pad to maintain the heat. A pad of absorbent cotton covered with oiled silk is about as good as anything. Or belladonna ointment may be applied on gauze, covered with cotton and retained in place by a bandage.

As previously mentioned, the subcutaneous or intramuscular injection of 20 to 30 cc. of convalescent serum may be effective in preventing orchitis. Should this develop the swollen gland should be supported and protected on a nest of absorbent cotton. In our experience hot compresses of a saturated solution of Epsom salts have proven efficacious. A 10 per cent solution of guaiacol in glycerin applied freely on gauze is highly recommended. Fougerousse[1] states that a diathermic treatment of one-half hour each day with precautions against the elaboration of too much energy often affords prompt relief and greatly

[1] Jour. Am. Med. Assn., 1925, **84**, 1117.

hastens resolution. With suitable apparatus it may be likewise applied to the parotids.

For the delirium, headache and restlessness of meningismus of severe cases an ice-bag should be applied to the head. Bromides may be given internally. Morphine may be required. Spinal puncture with the removal of 10 to 20 cc. of cerebrospinal fluid generally affords prompt relief and may be repeated. In meningitis spinal puncture is also required, and if suitable convalescent serum is available 10 to 20 cc. may be injected intraspinally, as it is the only specific serum or agent available for the treatment of mumps.

CHAPTER XX.

WHOOPING COUGH.

Definition.—Whooping cough or pertussis is an acute infectious disease of the respiratory tract characterized by spasmodic attacks of coughing, which in the later stages of the disease and in a long-drawn inspiration or "whoop."

Synonyms.—*Pertussis, chincough.* French, *Coqueluche.* German, *Keuch-husten.*

THE ETIOLOGY OF WHOOPING COUGH.

Bacteriological Aspects.—It is now generally agreed that the organism described by Bordet and Gengou in 1906 as the Bacillus pertussis is the cause of whooping cough. It is a small Gram-negative bacillus requiring special culture media for its growth. Its etiological relationship to the disease is based upon the frequency with which it is found in the upper respiratory tract during the catarrhal stage and the fact that specific agglutinins and complement-fixing antibodies are to be found in the blood after the third week of the disease; also by the results of prophylaxis and treatment with vaccines of the bacillus.

To the best of our knowledge the disease has not been experimentally produced in human volunteers by inoculation with pure cultures of organism, although Klimenko claims to have produced it in puppies and monkeys by intratracheal injections of the bacillus.

Meyer[1] has reported from the Serum Institute at Copenhagen 970 positive sputum cultures of Bacillus pertussis from 1106 cases as follows:

	Per cent positive.
Catarrhal stage	75
Paroxysmal stage (first week)	57
Paroxysmal stage (second week)	61
After fourth week	9

Povitzky,[2] using a medium acidified to a hydrogen-ion concentration of pH 6, obtained 38 per cent positive cultures in 26 cases.

Krumwiede, Mishulow and Oldenbusch[3] have identified two serological types of the bacillus (A and B) by agglutination reactions.

Recently Lawson and Mueller,[4] using a medium with a final titration

[1] Ugesk. f. Læger, 1921, **83**, 523; Acta pædiat., 1921, **1**, 99.
[2] Jour. Infect. Dis., 1923, **32**, 8.
[3] Ibid., 22.
[4] Jour. Am. Med. Assn., 1927, **89**, 275.

ranging between pH 6.6 and pH 7.3, reported an average of 41 per cent successful isolation of the bacillus in 533 cases. Of those examined in the catarrhal period, 59 per cent were positive, and the number of positives progressively decreased as the disease advanced. They have outlined methods by which cultures may be obtained to which reference will be later made. Nose and throat cultures, as usually taken, were not satisfactory. They did obtain results, however, by inoculating plates with sputum and by holding open plates of medium before the mouths of patients during paroxysms. Although the "cough plate" is useful when sputum cannot be obtained and when the child is old enough to understand the object of the work, the sputum culture will probably find wider favor. Anyone who is familiar with the procedure of obtaining sputum for typing in pneumonia could secure specimens satisfactory for use in pertussis. Thick, tenacious exudate from the trachea and bronchi is collected in a clean receptacle, such as a cup or a Petri dish. With the approach of winter, physicians who are within convenient reach of a clinical laboratory may find increasing use for this method of diagnosis. Its particular usefulness lies in the fact that the culture is more likely to be positive, the earlier in the disease that it is made. Barbier and Renard[1] and Lereboullet[2] also report that cultures are rarely positive after the fourth week of the disease, and this has an important bearing on epidemics, isolation and quarantine.

Quarantine for an arbitrary period of four to six weeks may be unnecessary in some cases. Lawson and Mueller advise culturing the sputum once a week, and when found negative to examine daily, quarantine being released when three negative cultures on successive days are obtained. The culture medium and technique employed are described later under Diagnosis.

General Aspects.—Whooping cough is of world-wide distribution. It is usually endemic in our large cities, but is apt to occur in widespread epidemics every two to four years. It is more severe in northern climates, possibly because of the higher incidence and severity of respiratory infections in general. While the disease may occur at any time during the year, it is most commonly seen during the winter and spring months.

Whooping cough may occur at all ages, but fully 80 to 90 per cent of cases are encountered in children of one to five years of age. It may occur in nursing infants and it has been stated that children have even been born with the disease in exceptional instances. Adults may be attacked and the disease has been known even among the aged.

Sex has some influence, inasmuch as females are certainly more frequently infected than males, and especially mothers, nurses and nurse-maids who are more likely to be brought into contact with

[1] Bull. et mém. Soc. méd. d. hôp. de Paris, 1922, **46**, 1592.
[2] Paris méd., 1919, **9**, 44.

infected children than men. Physicians are sometimes infected in case they have escaped the disease in childhood. Whooping cough in adults is frequently a serious disease

Infection and Dissemination.—Pertussis is most infectious during the catarrhal stage before "whooping" begins. This is borne out by clinical observations and likewise by the results of bacteriological investigations previously mentioned. When the paroxysmal stage has been reached the danger of infection is greatly reduced; also after the third week of milder infections which "whoop" only occasionally or not at all.

Since the bacillus occurs in the secretions of the respiratory tract, including the nose, it is almost surely spread by direct contact and "droplet" infection. During coughing the organisms may be secured in plates at a distance of one or more feet from the mouth. The bacillus is easily killed, and the danger of indirect infection thereby greatly reduced, but nevertheless it may be carried on fomites, especially on the clothes of attendants, and thus be communicated by a third person.

IMMUNITY TO WHOOPING COUGH.

The disease occurs only in human beings. Apparently some individuals are naturally immune and never contract the disease, even though exposed, although in some instances at least the immunity may be due to a previous unrecognized attack. Negroes are especially susceptible and the disease is more than twice as fatal among them.

One attack confers an immunity for the balance of life; second attacks are rare and when alleged to occur always involve the possibility that the first attack was not genuine whooping cough, since the protection afforded by this disease is probably greater than in any other acute infection. During the disease agglutinins, bacteriolysins, opsonins and complement-fixing antibodies are usually produced which render convalescent sera of some protective and curative value as well as rendering available agglutination and complement-fixation tests for the diagnosis of late atypical cases. Recovery is probably due to the action of these antibodies and especially to phagocytosis.

Agglutination Reaction. The agglutination reaction is sometimes of value in the diagnosis of atypical cases. Unfortunately it does not become positive earlier than ten days to two weeks after the onset of the disease, so that it fails to lend diagnostic aid in the catarrhal stage when mostly needed. According to Povitsky[1] and Worth,[2] the serum must agglutinate at least 1 to 200 for diagnostic purposes, since normal serum is said to agglutinate at 1 to 100. Bordet[3] states that agglutination tests are of value only when conducted with freshly isolated bacilli cultivated on a rich blood medium.

[1] Centralbl. f. Bakteriol., 1912, **56**, 276.
[2] Arch. Int. Med., 1916, **17**, 279.
[3] Berl. klin. Wchnschr., 1908, **45**, 1453.

Complement-fixation Reaction.—Positive complement-fixation reactions occur a little earlier in the disease than agglutination reactions, but usually not until the paroxysmal stage has been reached, and therefore too late to be of value in the diagnosis of the disease during the catarrhal stage. Park states that the sera of about 50 per cent of all cases yield positive reactions. An extensive literature has accumulated on the subject.[1] The test is also of value for differentiating Bacillus pertussis from other organisms resembling it morphologically and culturally by employing rabbit-immune sera. The sera of individuals treated with whooping-cough vaccine usually yield positive reactions.

Skin Tests.—It is possible that skin tests with Bacillus pertussis may be of some value in the detection of susceptibility and the diagnosis of obscure atypical cases. Modigliani and Villa[2] and Orgel[3] have described intradermal tests of this kind, but their work requires further study before an opinion of its practical value can be stated. Hull and Nauss[4] and Riesenfeld[5] have reported uncertain and unreliable reactions.

THE PROPHYLAXIS OF WHOOPING COUGH.

The seriousness of whooping cough by reason of its high mortality has not received the attention that it deserves. Nurslings and young children especially should be protected as much as possible; older children have much better chances of recovery.

Individuals with the disease should be isolated as soon as possible and quarantine maintained for at least six weeks until the paroxysmal stage has been well developed. Since the cough may persist for months, complete isolation for the entire period of the disease is not usually possible, but in institutions for children the subject is far more important than usually recognized and especially if measles is occurring, which greatly increases susceptibility to whooping-cough infection.

Every effort should be made to diagnose the disease as early as possible and to isolate promptly. Bacteriological and blood examinations are of distinct value as discussed later.

During the disease all sputum should be disinfected. Older children and adults should be required to cough into handkerchiefs in order to reduce "droplet" infection. It is to be hoped that *compulsory notification will enable the health authorities to obtain a better control on this very serious disease* and especially in institutions. Children with the disease should never be allowed to mingle with others in churches, "movies" or other places at any stage of the disease. After recovery it is advisable to disinfect the room and clothes of the patient.

Vaccination Against Whooping Couth.—Since whooping cough is usually spread during the early stage and frequently before it is sus-

[1] Kolmer: Infection, Immunity and Biologic Therapy, 3d ed., Philadelphia, W. B. Saunders Company, p. 555.

[2] Pediatria, 1921, **29**, 337.

[3] Jour. Am. Med. Assn., 1922, **79**, 1508.

[4] Ibid., 1923, **80**, 1840.

[5] Ibid., 158.

pected or diagnosed the subject of prophylactic vaccination has deservedly attracted considerable attention, and especially in view of the high mortality of the disease in institutions for children.

Freshly prepared vaccines have given the best results and at least three subcutaneous injections of *large doses* should be given at intervals of five to seven days before exposure or as soon as possible thereafter. For children the doses may be 500,000,000, 1,000,000,000,000 and 2,000,000,000,000 bacilli respectively; for adults, 1,000,000,000,000, 2,000,000,000,000 and 3,000,000,000,000 bacilli may be given.

Immunity is apparently produced in the majority of individuals by these large doses. Its duration is unknown, but probably is not over two or three years. Revaccination is apparently less effective.

We believe that this prophylactic immunization is well worth while not only in institutions but in families as well. Even though immunized individuals may contract the disease, and especially in epidemics, yet the attack appears to be much less severe, of shorter duration and with less danger of contracting pneumonia. Vaccination before exposure is more effective than after exposure and infection because several weeks are required for the full immunity response.

Hess,[1] Luttinger,[2] Huenekens,[3] Bogert,[4] Luzzati,[5] Davies,[6] Miller,[7] Bloom,[8] Spolverini,[9] Hammes,[10] McKibben,[11] and others have reported successful and encouraging results.

Serum Prophylaxis.—Since convalescent serum is known to contain antibodies affording protection for the balance of life in the majority of instances, it is highly probable that its injection will afford temporary immunity (four to eight weeks) against the disease in the same manner as measles convalescent serum is known to afford protection against that disease.

Debre[12] reports the successful prophylactic use of serum obtained from patients in the fourth week of the disease. In 40 cases 31 patients were entirely protected, 6 ran a very mild course and only 3 showed no apparent effect. The dosage was 3 cc. given intramuscularly.

In the case of nurslings and very young children this method of prophylaxis would appear to be well worth while, and if convalescent serum is not available we suggest the intramuscular injection of $\frac{1}{2}$ to 1 ounce of whole blood from a parent or other adult who has had the disease, as described for the prophylaxis of measles.

[1] Jour. Am. Med. Assn., 1914, **63**, 1007.
[2] Ibid., 1461.
[3] Am. Jour. Dis. Child., 1918, **16**, 30.
[4] Ibid., 1918, **15**, 271.
[5] Policlinico, 1920, **27**, 451.
[6] Am. Jour. Dis. Child., 1922, **23**, 423.
[7] Am. Jour. Pub. Health, 1921, **11**, 913.
[8] Arch. Pediat., 1919, **36**, 1.
[9] Policlinico, 1920, **27**, 1043.
[10] Deutsch. med. Wchnschr., 1921, **37**, 928.
[11] Boston Med. and Surg. Jour., 1923, **189**, 339.
[12] Bull. d. l'Acad. d. méd., 1923, **89**, 348.

THE INCUBATION PERIOD OF WHOOPING COUGH.

Owing to the insidious onset of the catarrhal stage, it is frequently impossible to state the incubation period of whooping cough in exact terms; it may be as long as two weeks and possibly as short as a few days. Probably in most cases it varies from one to two weeks; for practical purposes an individual who presents no evidence of catarrh fifteen days after the last exposure is free from the risk of contracting the disease.

THE SYMPTOMATOLOGY OF WHOOPING COUGH.

The disease is ushered in by a *catarrhal stage* usually lasting for one to two weeks, during which the patient presents the symptoms of an ordinary bronchial catarrh with persisting coughing of increasing severity. The cough is of a short dry type and occurs almost at any time, not showing at this early period the subsequent tendency to regular paroxysms. Toward the end of ten days, however, it becomes more severe and more paroxysmal, especially at night, and the patient often begins to vomit after a severe attack.

During this time the child is usually dull and listless, has a poor appetite, sleeps badly and in some cases there is sneezing, coryza and lacrimation. Sore throat is not uncommon, and cases are sometimes mistaken for diphtheria. Sometimes there is a slight afternoon rise of temperature.

The *paroxysmal stage* of four to eight weeks' duration now follows characterized by severe paroxysms of coughing of varying frequency and severity. They may be as few as one or two a day or as frequent as two or three every hour, with the general average of ten to fifteen per day during the height of the disease. The paroxysm is usually ushered in by warning signs of a sensation of tickling, constriction of the chest, yawning, sneezing, dizziness or some other sensation during which the patient breathes cautiously for fear of exciting cough, and, finally, when realizing it is inevitable, sits up or holds on to somebody or something or begins to cry which ushers in a series of rapid short machine gun-like expiratory coughs, as if trying to expel something from the larynx, followed by an interval during which the patient attempts to draw air in and, after a struggle, finally succeeds in inspiring, through the tense vocal cords which causes a prolonged crowing sound constituting the typical *whoop*. In a paroxysm there may be but one whoop in mild cases or as many as a dozen or more in severe cases. With the successive spasms the suffering of the patient becomes more acute. The face, at first flushed, becomes congested, purple and swollen. Tears flow from the injected and protruding eyes; strings of mucus, sometimes blood-tinged, hang from the nostrils, and a large amount is expelled from the mouth. The tongue, purple with congestion, protrudes from the mouth, and occasionally the sphincters relax with involuntary passage of urine and feces; prolapse of the rectum is

not uncommon. Vomiting usually terminates the attack, the child sinking back exhausted, sobbing and freely perspiring. In exceptional cases vomiting occurs at the onset. The whole process presents a very pitiable scene since the patients are usually so small, so badly frightened and obviously suffer so much as to enlist the deepest sympathies of the onlooker. As a result of the constant strain there is nervous irritability, and the face may become pale, swollen and puffy, with edematous eyelids, cyanotic lips and a weary expression. With frequent vomiting loss of weight is inevitable, and some infants die of marasmus; rickety and badly nourished children bear the strain poorly. The stomach is frequently filled with ropy mucus, which interferes with digestion and results in looseness of the bowels or even severe diarrhea. In older children, however, the general condition is usually good, if no complications are present, and between the attacks the pulse becomes normal, there is little or no temperature, the child plays contentedly and enjoys his meals.

Feeding should be done immediately after an attack as food just before a paroxysm is expected usually causes it to appear; this is sometimes a difficult problem because children may refuse food altogether because of a dread of the inevitable paroxysm. Coughing is most severe during the night, the patient awakening suddenly, sitting through the attack and sleeping between the spasms. Sometimes paroxysms may be prevented by suggestion, as threatened punishment or soothing encouragement, especially when whooping is maintained as a habit. In a hospital ward it is common to see many start whooping when a child begins an attack, probably from suggestion; or just the reverse will occur when the patients are interested in visitors or attendants.

Many cases develop an ulcer of the frenum, the result of mechanical injury to the under surface of the tongue. It is especially seen in young children who have erupted their two first lower incisor teeth; healing quickly occurs in convalescence.

Hemorrhages from the nose are not uncommon and streaks in the sputum are probably due to the rupture of minute bloodvessels in the congested respiratory tract. Blood may be swallowed and later appear in the vomitus. The terrific strain may also result in hemorrhages of the conjunctival and even of the edematous eyelids. Bleeding from the ears may occur as well as purpura of the skin in rare instances. Even meningeal and cerebral hemorrhages have been reported evidently caused by the high blood-pressure during paroxysms.

The duration of the *convalescent stage* is very variable, since whooping may persist for long periods of time even after the patient is quite well. Some children will whoop typically, though usually without vomiting, for months and even a year and especially if any bronchitis or an attack of measles follows the attack. The number of paroxysms gradually decrease to one or two a day, and usually occur at night. In some instances whooping is apparently kept up as a matter of habit.

COMPLICATIONS AND SEQUELÆ OF WHOOPING COUGH.

Complications of the respiratory tract are the most frequent and dangerous. Some *bronchitis* is present in all cases but does no harm as long as confined to the larger tubes. But *bronchopneumonia* is always likely to develop and, as in measles, is the most important and most fatal of the complications. In most cases this dreaded complication involves the posterior lobes and develops in the second to fourth weeks of the paroxysmal stage, but may occur as the patient enters upon convalescence when precautions are apt to be relaxed. With its onset the respiratory-rate rises rapidly, and in young children may reach 80 or even 100 per minute. The pulse-rate increases but not, as a rule, in proportion to the respiratory-rate. The temperature is variable and usually attains the highest point during the late afternoon or night. The usual physical signs are found in the chest; areas of pneumonia are apt to coalesce. Typical whooping generally ceases during the attack, but may return during convalescence; persistent cough continues with copious expectoration. Diarrhea and vomiting are commonly seen. *Lobar pneumonia*, however, is rare as likewise *pleurisy* with effusion.

Atelectasis is not uncommon due to the blocking of a tube with mucus during a paroxysm with sudden collapse of lung tissue. The patient falls back pale and cyanosed, the skin is cold and clammy and the respirations increased. Sometimes there is sudden syncope, convulsions or death.

Of course *emphysema* is always apt to occur with pneumonia and atelectasis and is usually to be found in the upper lobes. In very severe cases *pneumothorax* and even subcutaneous emphysema have been reported. *Bronchiectasis* has also been described.

Convulsions are always to be dreaded as they rank next to bronchopneumonia in relation to prognosis. They may be due to spasm of the glottis in severe cases accompanied by convulsive movements, aphyxia and unconsciousness. However, they may be seen in comparatively mild cases and especially in teething infants, who are frequently subject to nervous excitation from any small irritation. On the other hand, convulsions may be due to the influence of the toxins of whooping cough and especially of bronchopneumonia upon the meninges producing acute meningeal congestion, the so-called "serous meningitis" or "meningismus." The spinal fluid is increased and under pressure but perfectly clear, sterile and of normal cell content without increase of protein. They have also been attributed to meningeal and cerebral hemorrhages and thrombosis of the sinuses.

Children may continue to be nervous for a long period, are often easily frightened and any slight catarrh is liable to be mistaken for a recrudescence of whooping cough itself.

Cardiac dilatation is sometimes observed during the paroxysmal stage, and in some instances has left permanent damage and even

severe valvular disease. The *bronchial lymph glands* are usually enlarged, and one of the theories advanced to explain the mechanism of the paroxysms is pressure on the vagus nerves. Persistent enlargement may follow as likewise *chronic bronchitis*, *asthma* and *tuberculosis*. The last mentioned is especially to be dreaded after bronchopneumonia and sometimes runs a rapid course. *Otitis media* is not uncommon.

THE PATHOLOGY OF WHOOPING COUGH.

The Bacillus pertussis undoubtedly causes a tracheitis as the prominent lesion of whooping cough probably through the agency of toxins. These produce catarrhal and necrotic changes in the mucosa along with hyperemia and exudation in the submucosa. But the production of large amounts of mucus by the glands of the mucosa is a characteristic change and because of matting of the cilia with bacilli and secretions it gradually collects until it has to be expelled by a paroxysm of coughing.

This, however, is a common occurrence in other forms of tracheitis and bronchitis, and does not alone explain the paroxysmal character of the disease. Apparently the toxins are absorbed and display a special affinity for the nervous system and particularly for the vagus and recurrent laryngeal nerves as well as for the cerebral meninges. In other words, the paroxysms are apparently not due solely and entirely to tracheitis and bronchitis, but to the selective action of the toxin on the nervous system. Zangger attributes the paroxysms to the action of the toxins in the spinal cord with reflex action transmitted through the vagus nerves to the larynx and lungs.

Czerny and also Dobeli have regarded whooping cough as a neurosis and the paroxysms as the result of a "psychical infection." Dobeli goes so far as to state that the infected child must first have heard or seen the paroxysms of another. While suggestion, imitation and habit may have some influence upon the duration of coughing, yet it is ridiculous to assume that they have any influence upon isolated cases of the disease or in the production of paroxysms in infants under six months of age.

After death the lesions are principally those of bronchopneumonia, atelectasis, emphysema and enlargement of the bronchial glands in addition to the tracheitis and bronchitis. Meningeal congestion is sometimes seen as well as cerebral hemorrhages.

Blood Changes.—In 1897 Frohlich[1] called attention to more or less characteristic changes in the blood in whooping cough which are sometimes of aid in diagnosis. These consist of an early leukocytosis due principally to an absolute and relative increase of small lymphocytes. Meunier,[2] Grulee and Phemister,[3] Barach,[4] Mosenthal,[5] Kolmer[6] and others have reported similar findings.

[1] Jahrb. f. Kinderh., 1897, **44**, 53.
[2] Compt. rend. Soc. d. biol., 1898, p. 103.
[3] Arch. Pediat., 1905, **22**, 595.
[4] Arch. Int. Med., 1908, **1**, 602.
[5] Arch. Pediat., 1908, **25**, 831.
[6] Arch. Int. Med., 1909, **4**, 81.

It is true, however, that many other diseases are capable of causing leukocytosis and lymphocytosis of children, and furthermore both are higher in children than in adults under normal conditions; therefore, it is necessary to keep in mind the normal blood picture of children of various ages when using the total and differential leukocyte counts as aids in the diagnosis of whooping cough and the table employed by us is given later in discussing the diagnosis of this disease.

Of further interest in this connection are the *blood chemistry* studies of Regan and Tolstoouhov,[1] who observed in a series of 682 analyses a diminution of the total inorganic phosphorus associated with a lowering of the hydrogen-ion concentration of the blood, while the plasma bicarbonate remained within normal limits. These changes were observed early in the disease and bore no relation to the age of the patients but varied with the severity of the disease. In their opinion these changes indicate that an *acidosis* of an uncompensated type, which has as a cause the accumulation or increased concentration of free carbon dioxide in the blood, may be responsible for the vomiting of the disease as a means for eliminating acid in an attempt to maintain a normal acid base balance. The early administration of alkalis appeared to usually shorten the disease.

THE DIAGNOSIS OF WHOOPING COUGH.

The diagnosis of whooping cough during the *catarrhal stage* is always difficult and frequently impossible. During epidemics a bronchial catarrh with frequent irritating cough should excite suspicion and isolation. When the cough tends to become gradually worse and paroxysmal despite treatment with comparatively long intervals of relief, but with greater frequency during the night, the diagnosis becomes fairly certain and especially if vomiting occurs after the paroxysms. Measles can usually be excluded by the absence of a rash and Koplik's spots.

A total and differential leukocyte count is frequently of aid in diagnosis, although troublesome for the busy practitioner. In applying this examination it is necessary to keep in mind the normal blood picture of children of different ages, and we believe the following table of value in this connection:

Age.	Leukocytes.	Small lymphocytes, per cent.
3 to 12 months	11,000 to 13,000	45 to 46
1 to 2 years	11,000 to 12,000	41 to 42
2 to 3 "	11,000 to 12,000	35 to 36
3 to 5 "	10,000 to 11,000	27 to 30
5 to 10 "	9,000 to 10,000	25 to 28
Over 10 "	7,000 to 9,000	25 to 26

[1] Jour. Am. Med. Assn., 1926, **75**, 181 and 1116.

In the different stages of whooping cough Kolmer observed the following changes in children ranging from three months to four years of age:

Stage.	Total leukocytes.	Small lymphocytes, per cent.
Catarrhal	14,500 to 28,000	35 to 61
Paroxysmal	17,000 to 30,000	45 to 80
Marked improvement	12,000 to 35,000	32 to 50
Two months later	8,000 to 20,000	27 to 46

A well-marked leukocytosis with a definite and absolute increase of small lymphocytes for a child in *relation to its age* is always very suggestive and warrants isolation; therefore, blood examinations are particularly worth while in hospital practice.

In the *paroxysmal stage* diagnosis is ordinarily an easy matter unless typical paroxysms and whooping are absent. In such cases diagnosis is based upon the general explosive character of the cough, with no time for inspiration, which is worse at night, little or no fever and the presence of insignificant physical signs in the chest. Tuberculous bronchial glands are most likely to cause confusion, but can usually be detected by combined clinical and roentgen-ray examinations. An examination of the throat may excite a paroxysm and moreover it is necessary to exclude enlarged tonsil, as a possible cause of coughing. The presence of an ulcer of the frenum also tends to confirm the diagnosis although not pathognomonic of whooping cough.

The possibility of foreign bodies in the trachea may require consideration; laryngismus stridulus can usually be ruled out. But hysterical imitation is to be kept in mind and especially in institutions. In these the catarrhal stage is absent as likewise expectoration, vomiting, ulcer of the frenum and puffiness of the eyelids. Second attacks of whooping cough are extremely rare, and, therefore, a cough closely resembling it, in a person who has previously suffered from the disease, is almost certainly not a true case. Moreover some children acquire the habit of coughing during an attack which may afterward remain evident in an ordinary bronchitis.

Bacteriological Diagnosis.—While the isolation and identification of Bacillus pertussis is ordinarily a difficult matter, yet the method recently described by Lawson and Mueller may prove of practical value and especially in the detection of the disease in the catarrhal stage.

The Bordet-Gengou medium, which should be *freshly prepared*, is made as follows:

Five hundred grams of potato is passed through a coarse meat grinder and added to 1000 cc. of water and 40 cc. of glycerin. This mixture is shaken well and placed in an Arnold sterilizer for one hour. The resulting extract is pressed through cheese cloth in a small press, and to every 500 cc. of the resulting fluid 1500 cc. of 0.6 per cent salt solution and 50 gm. of agar are added. The medium is sterilized in the Arnold for one hour on three successive days. Following the

third heating, it is cooled to 42° C., and from 5 to 10 per cent fresh (not over seventy-two hours' old), sterile, defibrinated or citrated horse, human or rabbit blood added, and, after a gentle mixing, thin plates are poured. The end pH is from 6.6 to 7.3 after adding the blood.

When sputum is obtainable the more tenacious thick mucus is taken up on a platinum loop, washed thoroughly in three baths of sterile saline solution and plated by making a light even smear over an entire plate. With infants and young children from whom sputum may not be obtainable an open plate is held 5 or 6 inches in front of the mouth during a paroxysm. The former is the better method. Cultures of the nose and throat are of no value.

After two to three days' incubation at 37° C. Bacillus pertussis appears in minute, pearly-gray, translucent, regular, slightly raised colonies and resembling minute drops of mercury. Sometimes an incubation period of three to five days is required. If such colonies show a small Gram-negative bacillus they are transferred to tubes of the Bordet-Gengou medium described above, to "chocolate" agar and to plain infusion agar. If it grows only on the Bordet-Gengou medium it is regarded as Bacillus pertussis. Microscopic agglutination tests may be also employed, mixing a drop of culture with a drop of 1 to 10 normal serum and with a drop of 1 to 100 antipertussis serum.

With this method Lawson and Mueller observed 59 per cent positive cultures in 91 cases of whooping cough during the catarrhal stage and believe the method of value in the diagnosis of the disease. One negative culture does not exclude the infection, but with three negative cultures on successive days it is safe, in their opinion, to assume that whooping cough is not present.

THE PROGNOSIS OF WHOOPING COUGH.

Whooping cough is an especially serious disease among children under four years of age, and particularly among the undernourished children of the poor. Over 10,000 deaths are caused by it each year in the United States, and the mortality statistics from abroad have shown that from 13 to 35 children out of each 100 with the disease succumb to it. Among children of the better classes the mortality is much lower. The highest mortality occurs in children under two years of age; after ten years it is trifling, although the illness must be regarded seriously in aged individuals. Rickety children seldom do well and a weakly, badly nourished child under three years of age has a poor chance of surviving a severe attack.

As a general rule the longer the catarrhal period, the milder will be the paroxysmal stage due to better chances for developing immunity. During the height of the illness the gravity of the situation may be roughly estimated by the number and severity of the paroxysms, but if the child rests and feeds well between attacks the outlook is always

good. A sudden diminution of paroxysms is usually a bad sign and frequently indicates the onset of bronchopneumonia.

It is by all odds the most dreaded complication, because of the high mortality. Bad signs are pallor with cyanotic lips, extremely rapid respirations, restlessness and refusal to take food.

The development of convulsions is likewise of bad prognostic import.

Furthermore, the disease not infrequently lights up latent tuberculous lesions, and among tuberculous children the prognosis is always bad from this standpoint. Patients with enlarged tonsils, elongated uvulæ and adenoids are especially apt to be troubled by a return of paroxysms over a long period of time.

THE TREATMENT OF WHOOPING COUGH.

The essentials of treatment are fresh air, proper feeding and good nursing. Drugs and vaccines are sometimes useful adjuvants, but specific antisera are not available and the disease must run its course, while the patient is being nourished as best we may, given relief from the paroxysms and guarded as far as possible against the dreaded bronchopneumonia and predisposition to tuberculosis.

Unless the patient is quite sick and the paroxysms severe it is unnecessary to confine to bed. The clothing should be sufficient but over-clothing should be avoided in order to prevent sweating and chilling. A firm bandage around the abdomen and lower ribs to give support during the paroxysm is usually helpful and diminishes vomiting, especially in children under two years of age. It should be of elastic material, tightly applied and provided with shoulder straps to prevent slipping. We think it a good practice to rub the chest night and morning with camphorated oil and to apply a light jacket of flannel.

Plenty of *fresh air* is essential, although it need not be excessively cold air and draughts must be avoided. Hot medicated air has been tried and found wanting. During pleasant weather children should be placed out-doors; in winter the bedroom should be freely ventilated with fresh warmed air, and the patient kept warm and comfortable. Under these conditions they eat better, sleep better, are less nervous and show less tendency to develop bronchopneumonia.

They should be sponged or bathed frequently with due care against draughts. Zangger speaks highly of hydrotherapeutic measures in the treatment of neurotic cases, and especially of tepid packs at 54° to 60° F. The mouth, lips and nose should be kept clean and soothing ointment like that of zinc oxide applied to excoriations when present.

During a paroxysm an attendant should be with the patient if a child and support it, as it adds greatly to their misery to be left alone; mucus and vomited matter should be carefully collected and disposed of. Constipation should be corrected as paroxysms are always likely to become worse in the presence of alimentary irritation.

Feeding is not infrequently the most difficult problem of all, and particularly in young children and infants. This is especially true when the paroxysms are frequent and severe and followed by vomiting. Furthermore, children sometimes dread to take food for fear of exciting a paroxysm and even learn the trick of voluntary regurgitation. Emaciation must be avoided as much as possible, and here is where good nursing is indispensable. Frequent small feedings after paroxysms appear to be the best policy; over-feeding must be avoided. Even after vomiting the average child will eat again if given the opportunity as he should be. Children over five years of age do not usually present any difficulties and particularly if they are up and about. Their food may be the usual diet according to age, and if the appetite is capricious it is well to let them choose their food. Solid food is sometimes better than fluids, due care being taken against leaving crumbs in the fauces.

Younger children should be fed with milk, broths and soft foods according to age; whey is sometimes very useful for infants. A half-teaspoonful of whiskey once or twice during the day is frequently beneficial. Orange juice should be given routinely. Rectal feeding is so unsatisfactory that it should not be resorted to until every other plan has failed. Since vomiting may be due in part to acidosis, it is well to examine the breath and urine for acetone, and if present to give glucose syrup (Karo) with food and sodium bicarbonate (5 to 10 gr.) in ginger ale several times a day.

The *early* administration of *freshly* prepared vaccines in *adequate* dosage is undoubtedly efficacious in many cases in reducing the frequency and severity of the paroxysms, the duration of the disease and the danger of bronchopneumonia. Since first advocated by Graham,[1] in 1911, an extensive literature has accumulated upon the subject.[2] We employ a vaccine of Bacillus pertussis containing 2,000,000,000 per cubic centimeter or a mixed vaccine of Bacillus pertussis, pneumococci, staphylococci, streptococci and Micrococcus catarrhalis of the same concentration. A subcutaneous injection is given every three days, beginning with 0.1 cc. for children under five years of age (0.2 cc. for older children and 0.5 cc. for adults) and gradually increasing the dosage.

Unfortunately *antisera* are not available for treatment, although it is likely that potent immune sera may prove of value in lessening the toxemia. Bleyer[3] and Pentz[4] have used intramuscular injections of blood and serum from convalescents, and the results would appear to justify this treatment in severe cases, the technique and dosage being the same as described in the chapter on Measles.

Of course a large number of *drugs* have been tried. During the catarrhal and early paroxysmal stages a mild expectorant, like *wine of*

[1] Am. Jour. Dis. Child., 1912, **3**, 41.

[2] Kolmer: Infection, Immunity and Biologic Therapy, 3d ed., Philadelphia, W. B. Saunders Company, 1923, p. 975. Smith: Am. Jour. Dis. Child., 1924, **28**, 597.

[3] Am. Jour. Med. Sci., 1917, **154**, 39.

[4] Nederl. Tijdschr. v. Geneesk., 1917, **1**, 714.

ipecacuanha, in doses not exceeding 5 minims every four hours and just after coughing, may be given. For severe paroxysms the rectal injection of 10 cc. of *ether* in oil every eight hours has been recently recommended by Goldbloom,[1] Musser[2] and others. Subcutaneous injections are apt to cause sloughing. Its effects are due to excretion through the pulmonary alveoli; it is said to be a life-saving measure in infants. *Paregoric* may be given freely and especially to secure rest at night. Tincture of *belladonna* every four hours, until the pupils are dilated, is frequently helpful, although sometimes producing rashes; older children and adults sometimes object to the dryness of the fauces. *Bromides* are sometimes combined with it to advantage, although only moderate doses should be employed in order to avoid too much depression. *Antipyrin* is certainly efficacious for older children and adults, although unsuitable for weakly children. It is sometimes successful when belladonna fails. *Benzyl benzoate* by mouth is sometimes palliative and may be tried if other drugs fail to give relief. *Quinine* is useful toward the end of the paroxysmal stage for its tonic effects; 1 gr. for each year of a child's age may be given twice daily. In our experience local applications to the larynx of 2 per cent solutions of resorcin, 4 per cent antipyrin and 2 per cent silver nitrate have failed to be of any value.

Roentgen-ray applications to the chest have been advocated by Smith and his colleagues,[3] Bowditch,[4] Kingston and Faber,[5] Struthers[6] and McKibben;[7] in their opinion this treatment along with the administration of vaccines has proven efficacious, but Faber and Struble[8] have been unable to verify the results, and the treatment is still under trial; we have had no experience with it. The same is true of diathermy, ultra-violet light and inhalations of oxygen.

In *convalescence* cod-liver oil should be given and a complete change of air and scene by a few weeks at the seashore is excellent.

In the treatment of *bronchopneumonia* plenty of fresh air is advisable. The chest should be rubbed with camphorated oil and wrapped in a flannel jacket. Whiskey is usually helpful and careful feeding is required. Strychnine and digitalis may be indicated, but the former in very cautious amounts in order to avoid nervous excitability. The intramuscular or intravenous injection of 25 to 50 cc. of pneumococcus antibody solution has been helpful in some of our cases evidently due to secondary pneumococcus infection.

For *convulsions* a hot mustard pack may give relief. Spinal puncture with the removal of 10 to 20 cc. of fluid may give prompt relief in some cases when the pressure is high, but is not otherwise of value. Chloral and bromide may be given by rectum. A whiff of chloroform may be used to break prolonged spasms.

[1] Jour. Am. Med. Assn., 1925, **85**, 1791.
[2] Ibid., 1927, **88**, 1125.
[3] Ibid., 1925, **85**, 171.
[4] Ibid., 1924, **82**, 1422.
[5] California State Jour. Med., 1923, **21**, 429.
[6] Canadian Med. Assn. Jour., 1924, **14**, 141.
[7] Boston Med. and Surg. Jour., 1923, **189**, 339.
[8] Jour. Am. Med. Assn., 1925, **85**, 815.

CHAPTER XXI.

ERYSIPELAS.

Synonyms.—*St. Anthony's fire;* German, *Rothlauf* and *Rose.*

Definition.—Erysipelas is an acute infectious disease characterized by sudden onset with chills, fever and sometimes vomiting, and the development of a more or less characteristic cutaneous picture consisting of a sharply marginated edematous migrating eruption, with frequently the appearance of blebs. The disease is caused by infection with the Streptococcus erysipelatis.

History.—The history of erysipelas is coeval with the history of medicine itself. In Book III on *Epidemics,* Hippocrates describes an epidemic of this disease in such adequate terms as to enable us to definitely recognize it in its various stages. Celsus writes "that affection which I stated to be called ερυσιπελας (erusipelas) not only supervenes upon a wound, but occurs without one, and sometimes carries with it considerable danger, especially if it fix itself near the neck or head." It is generally stated that the first epidemic of erysipelas occurred in the United States in 1843, although Haser, in his *History of Epidemics,* alleges that erysipelas complicated the epidemic of smallpox in 1699.

THE ETIOLOGY OF ERYSIPELAS.

Bacteriological Aspects.—It is now generally accepted that a specific type of hemolytic streptococcus designated as Streptococcus erysipelatis is the cause of erysipelas. It has been long known that streptococci bore an important relationship to the disease, as likewise the fact that other hemolytic streptococci are capable of producing toxic erythemas sometimes resembling erysipelas, but it has been only during the past few years that convincing evidence of the specificity of Streptococcus erysipelatis has been furnished.

Birkhaug[1] has recently shown by means of agglutination and absorption tests that 91.2 per cent of erysipelas strains of hemolytic streptococci, isolated carefully from typical erysipelatous lesions, fell antigenically into one group, and that this group of streptococci could be readily differentiated by the same methods from strains of hemolytic streptococci isolated from scarlet fever, cellulitis, empyema, peritonitis, sinusitis, puerperal sepsis, tonsillitis and a number of other streptococcic infections.

[1] Jour. Am. Med. Sci., 1926, **86,** 1411.

By means of local passive immunity, Rivers and Tillett[1] successfully demonstrated that small areas of skin infiltrated with an immune monovalent streptococcic serum produced local protection against the culture of hemolytic streptococcus employed for the production of the serum, and that normal serum or beef infusion broth offered little or no protection against the injurious activity of the injected hemolytic streptococci. These authors concluded that the local passive immunity conferred by the immune serum naturally suggested the possible treatment of erysipelas by infiltrating the health tissues in the immediate vicinity of the erysipelatous margin with immune serum, on the assumption that when the infection spread to the prepared zone it would meet refractory tissues and be unable to progress farther. These studies were extended by Birkhaug[2] in order to determine possible antigenic relationships between erysipelatous and non-erysipelatous strains of hemolytic streptococci. It was demonstrated, by means of intradermal infiltration of the skin of susceptible rabbits with immune erysipelas serum, twenty-four hours previous to the injection of hemolytic streptococci of erysipelas and non-erysipelas origin, that the erysipelas serum offered adequate protection against 93 per cent of cultures of erysipelatous streptococci, and that almost no protection was offered by the erysipelas serum against the injurious action of non-erysipelatous hemolytic streptococci.

In subsequent studies Birkhaug[3] was also able to demonstrate that intracutaneous inoculation of hemolytic streptococci isolated from human cases of erysipelas produced typical erysipelas-like lesions in the skin of normal and susceptible rabbits. Again, it was found that intracutaneous infiltration of mixtures of immune erysipelas serum and hemolytic streptococci of erysipelas origin afforded local protection against the injurious action of the streptococci, and that normal rabbit serum or immune erysipelas serum heated at 60° C. for thirty minutes failed to protect the skin against the harmful effects of the inoculated erysipelatous streptococci. Further, it was demonstrated that intravenous or subcutaneous administration of large doses of immune erysipelas serum protected the animal against lethal doses of hemolytic streptococci isolated from erysipelas, when the serum was injected twenty-four hours before the bacterial inoculation and indicated that injections of large doses of erysipelas serum offered distinct promise for the specific treatment of the disease in man.

Clinical Aspects.—The older clinicians wrote prolifically and with divergent views on the influence of climate, season, soil, sex and similar factors upon the incidence of erysipelas. At the present day we know that these influences are in large part negligible, if not completely non-existent.

Erysipelas develops from the entrance of Streptococcus erysipelatis

[1] Jour. Exper. Med., 1925, **41**, 185.
[2] Bull Johns Hopkins Hosp., 1925, **37**, 85.
[3] Ibid., 307.

into the subcutaneous or submucous tissues. This infection usually is transmitted from another individual suffering from erysipelas. It is possible, however, that under certain conditions the disease may be autogenous, *i. e.*, developing in the patient himself. The infection usually takes place through some solution of continuity of the skin or mucous membrane, although the wound or abrasion may not be microscopically visible.

Trousseau found in all of his cases of facial erysipelas slight ulcerations or suppurations of the cavities of the nose or mouth or of the ear or tear passages, as the starting-point of the process. König found in 33 cases of spontaneous erysipelas, a slight injury as the probable entrance of infection in 19 of them, while in the others the examination was hindered by the tumefaction and inflammation of the tissues. Boring of the nose with the finger is a fertile cause of such infections.

Whether infection can take place through a perfectly normal skin or mucous membrane is a mooted question. Professor Garré, of the University of Tübingen, demonstrated years ago that infection of the uninjured skin with Staphylococcus aureus was possible. He rubbed into the skin of his arm a pure culture of the staphylococcus, developed 29 furuncles of a severe type and almost lost his life as a result of the experiment.

The old idea that erysipelas could be transmitted through the air is probably not true. When the disease spreads in the surgical or puerperal wards of hospitals it is apt to spread first to those in contiguity with erysipelas cases. The real source of the infection is infected hands of physicians, nurses, or attendants, infected instruments, dressings, utensils and hospital or household objects.

Apropos of spread of erysipelas in wards of hospitals, Campbell mentions a remarkable instance communicated to him verbally by Goodfellow and quoted by Volkmann and later by Zuelzer.[1] In the course of an epidemic of typhus fever in 1833 erysipelas broke out in a large ward containing 13 beds and attacked every patient in the sequential order of their beds.

König, of the Rostock Clinic, reported years ago a series of cases of erysipelas developing after operations in the amphitheatre. Pillows on the operating table saturated with blood were suspected. The pillows were extracted with water for twelve hours and rabbits then inoculated. One attempt was negative; in the other there developed at the site of inoculation upon the back a diffuse dermatitis which spread over the belly, produced an edema of the prepuce and bullæ and crusts upon certain areas, which disappeared after twelve days.

Age appears to have an influencing effect upon the incidence of erysipelas. This disease is not uncommon in infancy, owing to umbilical infections, and during the prime of life, although it may

[1] Ziemmsen's Cyclopedia of Practice of Medicine, vol. 2, p. 435.

appear at any age; among 12,556 persons who died of erysipelas in the years 1862–1868, 31.1 per cent were in the first year of life, 5.9 per cent were under five years of age, 2.9 per cent under fifteen, 4.2 per cent under twenty-five, 12.4 per cent under forty-five, 20.9 per cent under seventy-five, about as many under eighty-five years of age and 1.4 per cent were older.

In former times when *arm-to-arm vaccination* was in vogue, and when humanized crusts were carried around in the vest pocket by physicians, erysipelas was a not uncommon complication of vaccination.

Doepp[1] reports a remarkable transmission of erysipelas through vaccination. Lymph was taken from a child that was attacked a day later by vaccinal erysipelas, and 9 children vaccinated with it. All of the children developed erysipelas.

The late Dr. William M. Welch communicated to one of the authors (S) that for many years he had carried in his vest pocket a vaccinal crust between two glass slides. Vaccination with this crust produced erysipelas.

It would appear to be possible to contract erysipelas from patients dying of his disease through *postmortem examination*. Maclagen[2] and Rogez (1860)[3] have both quoted cases in which those making autopsies upon such cases developed the disease, although there was no discernible injury to the hands.

Many infectious diseases favor the development of erysipelas. In the epidemic of smallpox of 1901–1902 Welch and Schamberg observed among 2000 cases, 10 cases of erysipelas. Zuelzer saw this complication 7 times among 700 cases. In typhoid fever it occurred in 1 per cent of Murchison's cases; Zucharini saw it 18 times in 480 cases of typhoid and Zuelzer 3 times in 84 cases. In typhus fever Murchison mentions among 14,476 patients, 92 cases of erysipelas. Zuelzer saw it only twice among 229 cases. It is obvious that any debilitating disease which lowers the patient's resisting power facilitates to this extent the development of other infections, including erysipelas. It is really remarkable that one does not observe more often erysipelas as a complication of smallpox, considering the vulnerable condition of the skin.

As a complication of the puerperium, erysipelas, formerly a not uncommon accident, is growing less and less frequent as a result of rigid asepsis, the use of rubber gloves and the sterilization of all instruments, dressings, etc. The same statement applies with equal force to erysipelas after various surgical operations. Every now and then it will develop after *mastoid*, *nasal* or other operative procedure. It may also complicate ulcerated cutaneous cancer.

[1] Mitt. a. d. Arch. d. Gas. corr. Aerzte in Petersb., 1840; Schmidt's Jahrbuch, vol. **30**, p. 184.

[2] Edinburgh Med. Jour., 1837.

[3] Quoted by Zuelzer: Loc. cit., p. 435.

IMMUNITY TO ERYSIPELAS.

Disposition to erysipelas is widespread, but susceptibility is especially marked in the cases of recently delivered women, after injuries, burns and surgical operations.

One attack does not prevent subsequent attacks and recurrent erysipelas is noted in from 7 to 8 per cent of cases. A short attack apparently affords too little time for antibody production, but even though antitoxin is produced it would appear to disappear in as short a time as six weeks after recovery insofar as the duration of the immunity has been determined by Birkhaug by means of skin tests.

Recovery from erysipelas is probably due not only to the production of specific antitoxin but also to the production of opsonin capable of neutralizing the aggression of virulent organisms and promoting their destruction by phagocytosis.

Skin Tests.—Birkhaug, Amoss and others have observed positive skin reactions following the intracutaneous injection of the soluble sterile toxin of Streptococcus erysipelatis in susceptible individuals resembling positive Dick skin reactions. It is possible that this test may have a field of practical application for the detection of erysipelas susceptible individuals exposed to the disease in hospitals and other institutions when it is desired to give immediate passive immunity by the intramuscular injection of erysipelas antitoxin. At this writing it is not possible, however, to express the percentage of susceptible individuals of different ages, as sufficiently large numbers of persons have not yet been tested. The reaction is positive during the first few days of an attack of the disease, but after this time negative reactions may be observed due to the production of antitoxin.

Serum Prophylaxis of Erysipelas.—For this purpose 10 to 15 cc. of concentrated erysipelas antitoxin may be injected intramuscularly or subcutaneously. The immunity is believed to last about four weeks. Serum sickness sometimes follows which constitutes a drawback to the method, but in hospitals and other institutions where individuals and particularly surgical and obstetrical cases may be intimately exposed, it would appear worth while to attempt this passive immunization as soon as possible in addition to the immediate isolation of the patient.

Vaccination Against Erysipelas.—Recurrent erysipelas is observed in from 7 to 8 per cent of cases apparently due to the lack of sufficient antitoxin production for conferring protection to subsequent attacks or its disappearance after an attack of the disease, which may occur as soon as six weeks thereafter; positive skin reactions have been observed in such individuals following the intradermal injection of 10 skin-test doses of toxin.

Birkhaug[1] has advocated the active immunization or vaccination of

[1] Jour. Am. Med. Assn., 1927, 88, 885.

these individuals by subcutaneous injections of the toxins of Streptococcus erysipelatis, and reports that a group of 24 suffering with habitual attacks every six to twelve weeks and immunized by biweekly intramuscular injections of 500, 5000 and 50,000 skin-test doses of toxin have enjoyed a complete freedom from the disease over a period approaching two years. One of us has also observed similar results in 2 cases during the past year, but it is not possible at this writing to express an opinion of the value of the method until more experience has been gained.

THE SYMPTOMATOLOGY OF ERYSIPELAS.

Erysipelas is ushered in with chills, fever and inflammatory symptoms in the skin and subcutaneous tissues. There has been considerable controversy as to whether the local or the constitutional symptoms appear first. Trousseau states that the cutaneous manifestations very commonly precede the febrile symptoms. On the other hand, Roger contends that the reverse is the more common. In 500 cases observed by Roger severe constitutional symptoms appeared first in 310 cases. As a matter of fact, cases vary in this respect and the first observable symptom may be either a cutaneous eruption or fever and its accompaniments.

Location of Eruption.—The face and scalp are by all odds the commonest seats of the eruption, although various observers have had different experiences in this respect. Bird saw the face and head attacked 125 times in 260 cases, whereas the extremities suffered 135 times. This ratio is unusual and is quite different from that of most clinicians. Bardeleben states that there are 20 cases of erysipelas of the head to every 1 case elsewhere. Of 140 cases treated by Lenhartz, of Hamburg, 96 were cases of facial erysipelas, 23 of face and scalp, 17 wandering and 4 of the extremities. Among 597 cases observed by Roger, of Paris, the disease was limited to the face alone in 496; in 69 cases the face and scalp were attacked. The probable reason that the face is so often involved is not so much, as has been stated by some writers, that the tender skin of the face is most exposed to injuries, but because of the proximity of numerous cavities in which infection may take place. The hands are more often injured than the face and are certainly more exposed to dirt and infection. Chronic infections and ulcerations of the nose, ear, lacrimal sac, scalp, etc., offer ready ingress to the invading parasite. In 42 cases seen by Heyfelder the starting-point of infection was 12 times in the nose, 6 times in the ear, 5 times the eyelid, once the upper lip, 5 times the scalp, twice the lymph glands and once the mamma.

The mucous membranes themselves can exhibit evidences of erysipelas; the mouth, nose, pharynx, larynx, vagina and rectum may be primarily or secondarily attacked.

The navel of the new-born child is the chief site of infection in infantile erysipelas, a condition fortunately less common now than formerly.

Character of Eruption.—In facial erysipelas the eruption appears most commonly in the neighborhood of the nose or eyes.

The first local symptom is a feeling of heat, redness and tenderness or itching. A few small aggregated slightly elevated, reddened areas are soon seen. Increasing redness and swelling develop and peripheral spreading commences. The redness is at first but slight and somewhat maculated or in spots. Soon it becomes diffuse and much deeper in color. The swelling rapidly reaches a high degree, particularly in areas where the skin is thin and not bound down, as about the eyelids. The edematous areas are exquisitely tender to the touch. Owing to the edema and the consequent stretching of the skin, it appears *smooth* and *shining*. This and the sharply marginated, elevated spreading border constitute the most characteristic features of the eruption.

The progression of the eruption is nearly always in one direction, from the plateau-like elevated edge. This is doubtless due to the direction of migration of the invading organisms through the connective tissue and along the lymph paths. The non-spreading borders usually show no material elevation, the redness merging imperceptibly into the color of the surrounding skin. The spread is not a uniform advance, but more like that of an army going forward in different sectors. Billroth described these tongue or peninsular-like projections by comparing the spread of erysipelas with that of fluids infiltrating through blotting paper. The redness and swelling reach their greatest height on the second or third day, at which time in facial erysipelas the patient may be hideously disfigured. The eyelids are often so swollen that they cannot be opened. Soon a subsidence of inflammation sets in and the redness, edema and tenderness progressively lessen. Desquamation occurs, the epithelium coming off in grayish flakes or scales. This is a description of the course of the eruption in a given area, but progression of the eruption to other areas is the characteristic and usual insignia of the disease. While the eruption is running its course at one site it is slowly or rapidly spreading to the neighboring parts and there runs the identical course. The usual duration of facial erysipelas is from seven to fourteen days, sometimes longer. In obstinate cases the process may continue for three, four or five weeks.

Facial erysipelas may spread over the entire face and scalp but rarely progresses downward over the chin to the neck and trunk. The eruption may spread over the scalp to the occiput and then around to the neck and chest. Where the skin is denser and more bound down to the subjacent tissues, the erysipelatous process finds greater resistance to its progress. Thus at the chin, the base of the skull, the crest of the ilium, Poupart's ligament and the condyles of joints the eruption of erysipelas often stops and takes a more circuitous

route. Pfleger[1] states that the spread is influenced by the varying horizontal tension of the skin in different areas and that the "lines of tension" correspond with the long diagonal of the rhombic meshes formed by the connective-tissue bundles. Punctured openings in the skin are drawn in quite definite directions. The serum in the skin travels with least resistance in the direction of these lines of tension. Occasionally outlying erythematous areas are seen which may appear to some to arise *de novo*. The careful observer will usually be able to discern pale red streaks which connect these areas with the main body of eruption. In rare instances erysipelas may develop simultaneously in several separated sites. Volkmann, for instance, cites an instance of the synchronous development of erysipelas in two amputation stumps.

Bleb Formation.—In cases where the degree of inflammation is great it is common to observe the development of vesicles or blebs. The latter may reach the size of a five-cent piece or even a quarter dollar. The blebs are, however, flat, not hemispherical like those of pemphigus. The contents are at first serous but later become lactescent or frankly purulent. At times the fluid may be bloody. The blebs dry up and form flat crusts.

The neighboring lymphatic glands are almost invariably enlarged and tender. This adenopathy may occur extremely early in the course of the infection. It is even alleged that the lymphadenitis may precede the eruption, although this statement is not generally accepted. The glandular enlargement, however, forms quite a constant part of the erysipelatous picture. The glands subside quickly with the regression of eruption.

The rate of progress of the eruption is very variable. Within twenty-four hours the marginal spread may vary anywhere between 0 and 10 inches.

As a rule, the constitutional symptoms are proportionate to the severity of the eruption.

Erysipelas Migrans or Wandering Erysipelas.—Occasionally erysipelas assumes a wandering or migrating type and slowly or rapidly spreads over the entire trunk and extremities, healing in one area at the same time that it is advancing to virgin territory. The inflammatory process may even attack a given region a second time. These wandering forms are more prone to develop in association with erysipelas of the trunk or extremities than with facial erysipelas. In such cases the fever may be prolonged for several weeks or even months.

Fever.—The onset of erysipelas is ordinarily signalized by a chill, vomiting and a rapid rise of temperature to 40° or 41° C. (104° to 105.8° F.). While in general there is a parallelism between the extent of the eruption and the height of the febrile curve, one occasionally notes exceptions, in both directions, to this rule.

[1] Lectures on Surgical Pathology and Therapeutics, New. Soc., London, 1888, 2, 10.

The fever is usually higher in the evening than in the morning. In some cases it becomes remittent or, indeed, intermittent. Any sudden and pronounced rise of temperature usually indicates an extension of the disease or, indeed, if the cutaneous process has ceased, a relapse. In unfavorable cases the temperature remains high and may continue so to death or even thereafter. Frickinger, of Munich, states that 20 per cent of his cases ran an afebrile course, and Leube admits that in rare cases he has seen this. Roger,[1] among 570 cases, observed fever in only 315 and in more than one-half of these cases the fever only lasted three days. He, however, did not include cases in which a transient fever may have existed before admission to the hospital.

Czyhlarz[2] states that he observed 29 afebrile cases, all in women, among his 324 cases of erysipelas in one year.

Lenhartz affirms, however, that according to his experience every genuine erysipelas is accompanied by fever, and this has been our experience.

Lenhartz remarks that the elevation of temperature may be slight or of but short duration, but that it is always present if the *rectal* temperature is taken every few hours. In 140 cases studied by him the fever was as follows:

	Cases.	Average febrile period, days.
Facial erysipelas	96	7.90
Erysipelas of face and scalp	23	9.05
Wandering erysipelas	17	18.08
Erysipelas of the extremities	4	8.70

Other Systemic Symptoms.—In addition to fever, there is often headache, anorexia, furred tongue, nausea and commonly vomiting. In addition, there is marked prostration. The liver and spleen are often palpably enlarged, the former being at times tender. Occasionally diarrhea occurs and in very rare instances hemorrhage from duodenal ulcers may occur. These ulcers suggest the same causation as occurs at times in extensive burns.

Kidneys.—The urine is usually scanty and high colored at the height of the disease and may contain albumin. In severe cases casts and blood may be found. Acute nephritis is rather rare, but febrile albuminuria is common. Lenhartz observed acute nephritis 7 times, or in 4.7 per cent of 140 cases. Albumin may persist in the urine for some weeks after recovery.

Cerebral Symptoms.—Nearly all patients with erysipelas complain of headache and some of vertigo. These symptoms are more pronounced when the scalp is involved. Delirium is not uncommon even in cases not so severe. At times it may become violent and require physical restraint of the patient. Lethargy and stupor may be present

[1] Étude clinique de l'erysipèle; Rev. d. méd., 1896.
[2] Berl. klin. Wchnschr., September 11, 1911.

and patients may go into coma. In rare instances meningitis from a suppurating otitis or retrobulbar abscess may take place.

The Royal Prussian Army Report[1] states that among 1500 cases of erysipelas occurring between 1890–1892 there were only 2 cases of a purulent meningitis from an extension of the inflammation along the sheath of the optic nerve. Knapp collected 37 cases of blindness in the affected eye from retrobulbar inflammation in erysipelas.

Erysipelas of the Mucous Membranes.—As has been stated, the mucous membranes may be involved primarily or secondarily from cutaneous extension. The frequency with which coryza or an angina precede an attack of facial erysipelas suggests its origin at times in these structures, although not every precedent angina should be regarded as necessarily a true erysipelas.

Erysipelas of the mucous membranes with local and general symptoms which may be coincident or one may precede the other. Sometimes a severe chill and fever are rapidly followed by a marked coryza or sore throat and shortly afterward a cutaneous eruption at the border of the nostril or canthus of the eye. The extension to the skin takes place by continuity of tissue, either directly from the mucous membrane of the mouth through the posterior nasal spaces or the tear duct, or through the Eustachian tube and the external auditory canal to the skin.

The mucous membrane involvement consists of redness, swelling, violent local pain and swelling and tenderness of the adjoining lymphatic glands. Swelling of the uvula and epiglottis may occur. Ordinarily the appearances are not characteristic and the true diagnosis is made only when the typical eruption appears upon the skin.

It is claimed, however, that in rare instances the erysipelas may remain circumscribed to the mucous membranes. This may at least be surmised from a statement of Cornil that during an epidemic of erysipelas in Paris he had collected 18 such cases. Cornil regards as the characteristics of such erysipelatous angina the purple-red, shining, edematous, varnished-like appearance of the mucous membrane, the tonsils remaining free. There is great pain on swallowing, and at times it may be almost impossible to open the jaws.

The mucous membrane may also be attacked by extension of the process from the skin. The mucous membrane of the nose and mouth in facial erysipelas are usually red and swollen. Bass, in Wunderlich's Clinic, observed pharyngitis 32 times among 65 cases, in 9 cases there was great difficulty in swallowing.

Extension may occur to the larynx with the development of a serious edema of the glottis, necessitating at times a tracheotomy, which is, however, rarely successful.

A primary erysipelas of the larynx occurs in rare instances and is most fatal. The course is rather different from secondary involve-

[1] Sanitary Report for the Years 1884–1888.

ment. In this condition a chill and fever lasting several days may occur with difficulty in swallowing. The lymphatic glands become enlarged and painful and a lymphangitis, usually unilateral or marked on one side, occurs in the region of the thyroid cartilages.

On laryngeal examination there is a violaceous circumscribed edema of the glosso-epiglottic fossa which rapidly extends to the epiglottis and aryepiglottic folds. The erysipelas may remain limited to the larynx and may at times undergo regression. Or it may extend to the trachea, bronchi and lungs. Recovery has taken place particularly in the milder cases of laryngeal erysipelas.

Extension of erysipelas may take place to the lungs. "Erysipelatous pneumonia" is referred to particularly by Waldenburg and by Friedrich, who have called attention to the relation between peculiar forms of pneumonia and erysipelas. The disease has a marked tendency to spread from one lung to another, like wandering erysipelas. An interesting case was reported by Mosny,[1] who saw a pneumonia in a domestic of a man who had facial erysipelas. The outcome was fatal and at autopsy a circumscribed bronchopneumonia was found from which pure cultures of streptococci were obtained which produced a true erysipelas in the ear of a rabbit.

Erysipelas of the Female Genital Tract.—The puerperal woman is in greater danger of erysipelas than other women, an observation which made the older accoucheurs avoid contact with erysipelas. For it was found that a fatal puerperal infection was carried to the genital tract. The starting-point of erysipelas is usually at the external genitalia through some laceration or abrasion. The onset is heralded by chill and fever and then an eruption appears in the vulva or surrounding parts and spreads upward over the abdomen or over the nates or the thighs. The vulva may be so greatly swollen as to become necrotic. The erysipelas may likewise spread up the genital tract. The extension through the uterus and Fallopian tubes may give rise to peritonitis. It is only in cases in which characteristic cutaneous involvement takes place that a definite diagnosis of an associated erysipelatous peritonitis can be made.

Erysipelas Neonatorum.—Erysipelas of the new-born was formerly much more common than at the present day. Not only does the healing navel offer a site for the infection, but the thin and tender skin of the infant is also vulnerable. Puerperal infections are fortunately much rarer than in former times, and a relationship appears to exist between such infections and erysipelas in new-born infants. The infection tends to spread rapidly over the trunk involving the extremities and even the face. The patient may die from exhaustion, from umbilical phlebitis or from peritonitis. Frequently the cutaneous redness and swelling are but slight, symptoms of peritonitis dominating the picture and often being the first sign. The prognosis in earlier

[1] Semaine méd., 1890, vol. 7.

times was extremely bad. Steiner had only 2 recoveries among 80 cases. Billard saw 16 recoveries among 30 cases. After three months of age the chances of recovery are better. Modern treatment renders the prognosis in infantile erysipelas distinctly more hopeful.

Relapses and Recurrences.—Clinical experience strongly suggests that erysipelas does not leave after recovery protective antibodies in the blood. Indeed, an erysipelas patient is more subject to the disease than one who has not had it. The experience of many physicians and surgeons shows that in quite a proportion of cases erysipelas tends to recurrence. Relapses occur after an interval of days, whereas the term recurrence is applied if the *interim* between attacks is weeks, months or years. Of the two, relapses are in general commoner. Lenhartz observed 7 relapses among his 140 cases; in 27 cases there was a history of previous attacks. Roger encountered 10 per cent of relapses and 27 per cent of recurrences. In Fricklinger's group of 528 cases, there were 208 recurrences. Of these 116 had two and 92 had three or more attacks.

A woman under the care of Hirtz and Widal[1] had 20 relapses within a period of three months. Some were of short duration but others were accompanied by grave symptoms.

THE COMPLICATIONS AND SEQUELÆ OF ERYSIPELAS.

Boils and *abscesses* are not infrequent complications of erysipelas. Zeller and Arnold saw a case in which 650 furuncles occurred during the course of fifteen months. They occur usually upon areas which have been the seat of the erysipelatous process.

After recovery from erysipelas the *hair of the scalp commonly falls.* The hair is ultimately completely restored unless deep abscesses have been present upon the scalp.

Occasionally one sees more or less extensive phlegmonous infiltrations. Extensive *gangrene* of the skin is a rare but grave complication and may initiate or accompany a general septic poisoning. Gangrene particularly when severe is fortunately a rare complication. The Royal Prussian Army Reports state that among 1491 cases this complication occurred only 4 times. The areas involved are usually those over a bony structure, where there is little fat for protection.

Pneumonia, pleuritis and peritonitis occur at times as sequelæ. In rare instances pyemia may develop with accompanying *purulent arthritis* of the knee or other joints.

Complications attacking the *eyes* and orbits occur from time to time. There may be gangrene of the lid, impairment of vision, transitory blindness, panophthalmitis with suppuration and atrophy of the globe, iritis, retinitis, ulceration of the cornea, optic neuritis, etc. Fortunately these complications are rare.

[1] Deutsch. med. Wchnschr., 1892, p. 464.

The *auditory* apparatus may also be occasionally attacked during facial erysipelas, producing inflammation and suppuration of the auditory tract or a similar process in the parotid gland. Parotitis occurred only twice among 140 of Lenhartz's cases, but otitis media was more frequent.

Suppuration of the *frontal sinuses* or the *antrum of Highmore* has occurred in rare cases. Violent and persistent frontal headache should lead to a suspicion of the former condition.

Heart.—According to Teissier,[1] erysipelas quite frequently influences the myocardium. Among 500 patients, myocardial changes occurred in 250, dilatation in 44. With recovery the signs disappear, without permanent injury.

Endocarditis may also occur and may be followed by a persisting valvular lesion. Sir Dyce Duckworth and Hall White report a number of cases, although they regard the occurrence as rare. Achalone, however, quoted by Thoinot, believes that these heart complications are relatively frequent.

THE DIAGNOSIS OF ERYSIPELAS.

Classic erysipelas is an easy disease to diagnose. The characteristic symptoms are a sudden onset with chill and fever and an edematous reddish swelling of the part affected. *Centrifugal extension* with an *elevated wall-like margin* cannot hardly be confounded with anything else. The inflamed areas are exceedingly *tender* to slight pressure.

We have frequently seen acute *erythematous eczema* with great swelling of the eyelids diagnosed as erysipelas. These cases are, however, afebrile, and while erysipelas is alleged to occasionally exist without fever, it would not be cases of this type.

Erysipelas may be confounded with an acute lymphangitis which may be accompanied by swelling, redness, pain and fever. Such a condition usually occurs upon the extremities and may exhibit a streaked or spotted redness but not the confluent type seen in erysipelas. Usually a cord-like infiltration of the lymphatic vessels can be felt.

Acute diffuse *phlegmon* may be associated with fever, pain, redness and swelling, but instead of the pitting edema of erysipelas there is hard board-like infiltration, and the redness fades into the surrounding skin instead of being sharply marginated.

Malignant pustule or *anthrax* on the nose may present a superficial resemblance to erysipelas, but the spread is much less rapid, and cultural and microscopic examination will definitely differentiate this condition.

Erysipeloid of Rosenbach is characterized by an eruption on the fingers or hand which very slowly spreads from the site of infection. There is a sharply defined, slightly elevated, dark violaceous, almost

[1] Semaine méd., January 12, 1910

livid red spreading border. Constitutional symptoms are usually absent. Spontaneous recovery takes place in one, two or three weeks. It occurs in cooks, kitchen workers and butchers and is due to a wound with dead animal matter of divers nature. It is common after crab bites.

Klauder[1] describes a form of erysipeloid in fishermen which is more severe in character and which exhibits a deep spreading erythema, with considerable pain, lymphangitis and glandular swelling with or without suppuration. Fever and constitutional symptoms may be present. The disease runs a course of three to four weeks.

Klauder and Harkins, working in the Research Institute of Cutaneous Diseases, in 1926, were able to grow from excised sections of skin in this condition the bacillus of swine erysipelas. This latter affection is an acute septicemic infectious disease of young hogs caused by a fine rod-shaped bacterium—Bacillus erysipelatis suis. Ninety-seven cases of swine erysipelas have been collected by Ders as occurring in man from accidental inoculation, chiefly from handling cultures. Acél[2] recovered the bacillus from 5 cases of erysipeloid.

Erysipelas Mitis.—A condition is not uncommonly seen upon the legs or at times on the scrotum and penis in which there is swelling, redness and pain accompanied by an elevation of temperature to about 100° or 101° F. but without prostration. This condition is distinctly *recurrent,* attacks taking place very four weeks to six months. Some patients suffer from so many attacks that they are unable to plan their activities for any period of time in advance. The site of infection is often an eczema between the toes or on the foot or about the genitalia. The symptoms persist for about a week. The syndrome is so mild that we would suggest for this form the designation *erysipelas mitis.* After subsidence of the inflammation the leg or scrotum remains larger than before. Repeated attacks may produce a condition resembling elephantiasis.

A somewhat similar recurrent form of erysipelas mitis is often seen on the sides of the nose or cheeks, from intranasal infection. There is but slight fever and no tendency to extension of the eruption.

THE PROGNOSIS AND MORTALITY OF ERYSIPELAS.

Despite the fact that patients with erysipelas appear to be gravely ill, the mortality is relatively low. Zuelzer collected records of 10,000 cases from different writers and calculated the fatality to be 11 per cent. Certain authors have had a considerably smaller mortality-rate. Blass' rate was 3 per cent; Volkmann (Halle), 5 per cent; Ritzman (Berlin), 7.8 per cent; Heyfelder (Petersburg), 10 per cent; Roger (Paris), 4.53 per cent.

Before the age of three months the disease is particularly fatal. In

[1] Jour. Am. Med. Assn., 1926, **86**, 536.
[2] Deutsch. med. Wchnschr., 1924, **50**, 988.

very aged people the disease sometimes runs a mild course. Schlesinger[1] had a mortality of 25 per cent of his 288 cases in the elderly, but only 2 patients out of 15 over eight years of age succumbed.

THE TREATMENT OF ERYSIPELAS.

At the outset of this section we desire to issue the caution that in a disease which ends favorably in about 90 per cent of the cases, and which runs a most capricious course, deductions as to the therapeutic value of any medicament or special method of treatment must be subjected to the most rigid criteria and the strictest scrutiny.

The natural tendency of the disease is to get well and a therapeutic procedure can only be heralded as effective if it reduces the severity of the symptoms and brings about recovery in more than 90 per cent of the cases.

Local Treatment.—The number of local remedies that have been recommended in the treatment of erysipelas is legion, and as is usually the case, the number of agents advised in the treatment of any given condition is in inverse proportion to their efficacy. To influence a a deep-seated condition like erysipelas from the exterior, the remedy must either possess a power of great penetration or it must in some way increase the general resisting power of the patient. None of the external medicaments advocated answer these requirements. To be sure there are some which are capable of lessening the inflammation in the skin and of increasing the comfort of the patient.

We will briefly pass in review some of the older remedies, mentioning them merely to discourage their use.

Hueter, Neudörfer and others employed with alleged benefit daily subcutaneous injection of 10 to 20 drops of a 1 to 2 per cent solution of carbolic acid beyond the spreading border of the patches. This treatment is now forgotten.

Iodoform, carbolic acid and all manner of substances have been incorporated in salves and pastes and smeared on the affected parts. A more recent fetish is the use of ointments of ichthyol. This is not only dirty and nasty smelling, but it creates such a low visibility that the physician is not able to judge of local progress or extension.

Much preferable is the use of evaporating liquids in the form of compresses. Solutions of magnesium sulphate have been much employed, but we prefer the following:

Hydrargyri bichloridi		0.2
Acidi borici		20.0
Glycerini		80.0 cc.
Vini rectif.		200.0 cc.
Aquæ	q.s.	1000.0 cc.

This lotion contains 1 to 5000 of corrosive sublimate which is certainly an excellent antiseptic. The boric acid increases the sooth-

[1] Med. Klin., August 8, 1909.

ing properties of the combination. The glycerin lessens the tendency to excessive drying of the skin, and the alcohol is penetrating and reduces inflammation through its evaporative and cooling effect.

Masks made of lint with opening if necessary for the eyes, nose and mouth may be kept continuously applied. The application is comfortable and clean, and permits of an unhindered inspection of the parts daily.

In *migrating* erysipelas of the extremities a number of agents have been employed with the idea of checking the spread of the eruption. Many physicians have believed that they saw good results from painting the area beyond the spreading border with tincture of iodine or nitrate of silver. It has been suggested that this is much like painting a magic circle to charm the streptococcus into submission. Another method for which much has at times been claimed is the painting beyond the border with contractile collodion or constricting with adhesive tape. If it could be proven that the streptococcus could not pass the limits of this constriction then a reasonable basis for such a method could be laid. Avata and Woodyatt[1] have applied with a cotton swab or brush non-flexible collodion so as to form a continuous stripe $\frac{1}{2}$ inch wide and from $\frac{1}{2}$ to 1 inch in advance of the induration. so as to completely circumscribe the infected area. The stripe was painted over repeatedly until, when dry, a constricting furrow from $\frac{1}{2}$ to $\frac{3}{4}$ inch deep, and unbroken at any point, completely surrounded the diseased area. Breaks or cracks were repaired from day to day. It was observed that the inflammation did not advance beyond which was ascribed to complete constriction of the lymphatics and to materially shorten the course of the disease.

Physical Agents.—Within recent years light rays have been tried in erysipelas. Finsen employed carbon-arc red light much in the same way as he did in the treatment of variola. The results were indifferent. Some years later Aristide and Müller both used the same method and were much impressed with the results, although it is doubtful if the interpretations were sufficiently critical.

König, in 1913, appears to have been the first to try ultra-violet light, although the results were published only in 1916.[2] He was not particularly impressed by the results, and thought that in some cases the induced erythema aggravated the condition. During the World War, owing to the great prevalence of erysipelas, many central European physicians tried out this treatment. Beck, Carl, and Cappelle each reported excellent results in severe infections. They state that improvement takes place after the first exposure. Exposures were given daily for ten minutes at a meter's distance.

Schenck-Popp treated 18 cases in 1919 with the mercury quartz lamp. The treatment seemed effective in superficial cases, but failed when the lymph channels were involved.

[1] Jour. Am. Med. Assn., 1918, **71**, 900.
[2] München. med. Wchnschr., 1916, **63**, 1701.

Petenyi treated 14 cases of infantile erysipelas, 5 of them newly born. There were 2 deaths, the others showing striking improvements.

Czepa[1] treated 100 cases with most favorable results. He claims that in 100 per cent of the cases, fall of temperature and cessation of spread occurred after the first exposure. A favorable report is similarly published by Brünaver.

It should be emphasized that ultra-violet light under the most favorable circumstances does not penetrate more than a fraction of 1 mm. into the skin; therefore, any beneficial effect in a deep process would have to come about from a stimulation of the defensive mechanism of the body.

Roentgen-rays in Erysipelas.—The first report on the use of roentgen-rays in the treatment of erysipelas appears to have been published by Magelhaes, a Brazilian physician, in 1915. One of the authors of this volume (S), however, used the roentgen-rays in a desperate case of recurrent erysipelas in an influential citizen of a town in the middle west in 1905. The patient, who was sixty-eight years of age, recovered and lived to the age of eighty-two years. The second patient was treated in 1927. This case was in a young woman who had had a severe mastoid operation. About the fifth day the temperature rose to 104° F. and an erysipelatous eruption appeared on the face. After three $\frac{1}{4}$-unit skin doses of the ray were applied to the face the process at the end of three days ceased and the patient made a good recovery.

Magelhaes[2] used the rays with striking success in a case of erysipelas complicating skin carcinoma. He himself contracted erysipelas and was successfully treated. He subsequently treated 9 more patients, some of them refractory and recurrent cases. This agent appeared to him to be unusually effective. In 1917, Schmidt[3] reported 28 cases treated with roentgen-rays, and Hesse[4] 43 cases with favorable results. Most of the patients exhibited improvement after the first or second exposure as evidenced by abrupt fall of temperature, cessation of edema and marked improvement in the general condition.

Haidenhain[5] treated 30 cases of erysipelas of the face and scalp with somewhat less favorable results. In 20 cases there was marked benefit. He believed his mediocre results were due to the employment of too weak a dosage.

Platou, Schultz, and Collins[6] reported the results of treatment in erysipelas with the roentgen-rays alone and combined with specific erysipelas antitoxin. Eighty cases were treated with roentgen-rays, 30 with antitoxin, 10 with the two combined and 35 control cases not treated by these methods.

The efficacy of the roentgen-ray is attested by prompt return to normal temperature (1.5 days in irradiated group as compared with

[1] Wien. klin. Wchnschr., 1922, **35**, 564.
[2] Mém. Acad. nationale de méd. de Brésel, May 21, 1916; Para médico, 1917, vol. **1**.
[3] München. med. Wchnschr., 1917, **64**, 1144. [4] Ibid., 1918, **65**, 505.
[5] Strahlentherapie, 1926, **24**, 37.
[6] Am. Jour. Dis. Child., 1927, **34**, 1030.

3.4 days in control group), and by the more rapid disappearance of such symptoms as pain, toxemia and general malaise (two days in irradiated group as compared with eight days in control group). Extension of disease occurred in 21 per cent of the irradiated group as compared with 68 per cent in the control group. Extension in the former group was slight.

The mortality among the roentgen-treated patients was 6 per cent; in the control group, 23 per cent. The authors believe that antitoxin and roentgen-rays are both of definite value and should be used conjointly. Successful results followed the use of antitoxin and roentgen-rays in 10 cases in which the prognosis was considered especially grave from the point of view of age of the patient and extent and severity of the disease. The involved areas and the contiguous normal skin should be irradiated.

Serum Treatment.—As a result of the intensive investigations on the specificity of Streptococcus erysipelatis and the demonstration of its toxin-producing qualities during the past few years, interest in the serum treatment of the disease has been greatly renewed and improved so that it may be now stated that the administration of erysipelas antitoxin should be a part in the treatment of at least all severe infections. Indeed, we believe that the serum should be given the majority of cases in order to shorten the attack as quickly as possible and because even mild ones may become severe or recurring.

At the present time concentrated serum is available which greatly reduces the incidence and severity of serum reactions. As a general rule, the serum is given by *intramuscular injection* in dose of 10 to 40 cc. and several doses at daily intervals are generally required for all except mild infections. In severe fulminating cases intravenous injections may be required in order to neutralize the circulating toxins as soon as possible. Anderson[1] has recently described a method of preparing the antitoxin and Birkhaug[2] has described a method for standardizing the serum, although an official unit of strength has not yet been adopted. All sera, however, are carefully tested by the makers and the doses advised are generally satisfactory.

Even ordinary polyvalent antistreptococcus serum has been used with some success for many years and more recently by Lavender[3] and by Goresco and Popesco.[4] Convalescent immune serum has likewise been used by Kaiser,[5] Jordan and Dustin[6] and others, but much better results have been reported within the last year or two from the use of specific erysipelas antitoxins and our own experience with them have been much more favorable than observed with ordinary polyvalent antistreptococcus sera.

Birkhaug[7] have observed in the treatment of 60 moderately severe

[1] Jour. Lab. and Clin. Med., October, 1927.
[2] Jour. Infect. Dis., 1928, **42**, 35.
[3] Ohio State Med. Jour., 1924, **20**, 697.
[4] Compt. rend. Soc. de biol., 1925, **92**, 291.
[5] Arch. Pediat., 1915, vol. **32**, No. 7.
[6] Jour. Am. Med. Assn., 1924, **82**, 874.
[7] Ibid., 1926, **86**, 1411.

cases that the intramuscular injection of 100 cc. of the unconcentrated and from 15 to 20 cc. of the concentrated erysipelas serum, when administered during the first three days of the disease, caused a prompt amelioration of toxic depression, a critical fall in temperature and pulse-rate, prompt fading of the erysipelatous lesion, and rapid absorption of the blebs and edema within the affected areas. In late cases the results were strikingly favorable in ameliorating the general toxic depression, although repeated injections were sometimes necessary completely to neutralize the circulating toxin in the patient's blood.

Musser[1] has likewise observed good results and Symmers and Lewis[2] state that in a series of 131 cases treated with intramuscular injections of serum in the Bellevue Hospital of New York, the length of the hospitalization was reduced over 53 per cent. Of the 111 cases of facial type, 85.6 per cent were cured in from three to seven days and 9.9 per cent in from eight to twenty-one days, with a mortality of 4.5 per cent. In the 92 cases of facial type treated without antitoxin 33.7 per cent were cured in from two to seven days, 47.8 per cent in from eight to eighteen days and 12 per cent in from twenty-three to fifty-four days, with a mortality of 6.5 per cent.

Of 20 cases of body type, 60 per cent were cured in from three to seven days and 30 per cent in from eight to sixteen days, with a mortality of 10 per cent. Of 15 cases of body type treated without antitoxin, 46.6 per cent were cured in from seven to fifteen days, and 13.3 per cent in from twenty-five to fifty-eight days, with a mortality of 40 per cent. The mortality-rate over a period of twenty-three years at Bellevue Hospital for erysipelas was 10.1 per cent, whereas in the present series it was but 5.3 per cent.

In severe infections streptococci may be found in the blood in cultures and in these the prognosis is more unfavorable. Very careful examinations should be made each day for localized collections of pus which should be incised and drained without delay. Intravenous injections of serum are usually required in dose of 50 to 100 cc. and blood transfusions are sometimes helpful. *Chemotherapy* may be likewise indicated, and Young and Birkhaug[3] have reported successful results following the intravenous injection of mercurochrome in dose of approximately 23 cc. of 1 per cent solution per 100 pounds of weight. Young, Hill, and Scott[4] also report the successful treatment of 7 additional cases with mercurochrome, and it would appear well worth while to try this compound in severe cases rebellious to serum treatment. We have had no encouraging results with intravenous injections of gentian violet or neutral acriflavine. Rivanol (an acridin dye) and vuzin (a quinine compound) have been employed abroad, but we have no experience with them.

Vaccine Treatment.—Vaccine treatment has generally failed to influence the disease and probably most physicians are opposed to the

[1] Jour. Am. Med. Assn., 1927, **88**, 1126.
[2] Ibid., **89**, 880.
[3] Ibid., 1924, **83**, 492.
[4] Arch. Surg., 1925, **10**, 813.

use of vaccines in acute erysipelas; it cannot be denied, however, that when vaccines have been employed *early* in the infection, that not infrequently the lesions and symptoms have rapidly subsided. Owing to the self-limited character of erysipelas it is not always easy, however, to evaluate the worth of a therapeutic measure. Because of the difficulty and delays in obtaining the streptococcus in pure culture, it is necessary to employ a stock streptococcus vaccine for a time at least. During the acute stage the doses should be small, beginning with 0.1 cc. of a vaccine containing 500,000,000 killed streptococci per cubic centimeter; the injections should be given subcutaneously every five days and in gradually increasing amounts.

In chronic and recurring erysipelas vaccine therapy is more strongly indicated; the dosage and intervals of injections should be as stated above until 1 cc. of vaccine is being given at one time.

Non-specific Protein Therapy.—Lambert,[1] Hess and Dwyer[2] and others have reported favorably upon the subcutaneous injection of 10 to 15 cc. of leukocytic extract once a day for several days in the treatment of acute erysipelas.

Petersen[3] has reported that the intravenous injection of 0.5 to 2 cc. of a 2 per cent solution of proteoses has yielded very satisfactory results; also the administration of milk and typhoid vaccine. Holler[4] has employed intravenous injections of deutero-albumose, but the doses must be small in order to avoid severe general reactions which are readily induced (not over 0.1 to 0.5 cc. of 1 per cent solution). Blumenau[5] has employed nuclein injections; sodium nucleinate may be injected subcutaneously in dose of 0.5 gm.

Schmidt,[6] Ledbetter[7] and others have employed intramuscular injections of 5 to 10 cc. of market milk boiled for ten minutes and cooled.

Normal horse serum and diphtheria antitoxin have been employed, especially by the French clinicians, in dose of about 10 to 20 cc. by subcutaneous injection.

Our impression is that these non-specific agents are especially indicated in chronic and recurrent erysipelas; great care must be exercised in dosage because of the chances of eliciting severe general reactions.

Intramuscular injections of blood have been employed by Deacon[8] and Pines;[9] Schaffer and Rothman[10] have found blood transfusions of value in the treatment of erysipelas of children.

[1] Am. Jour. Med. Sci., 1909, **137**, 506.
[2] New Jersey Med. Rec., 1913, vol. **71**, No. 11.
[3] Protein Therapy and Non-specific Resistance, Macmillan Company, 1922, p. 191.
[4] Med. Klin., 1917, **13**, 1038.
[5] Ztschr. f. Immunitäts., 1911, **3**, 1075.
[6] Med. Klin., 1916, **12**, 171; 1920, **16**, 691.
[7] Canadian Med. Assn. Jour., 1924, **14**, 1179.
[8] Brit. Med. Jour., 1925, ii, 1059.
[9] Ibid., 1926, i, 95.
[10] Am. Jour. Dis. Child., 1927, **33**, 116.

CHAPTER XXII.

CEREBROSPINAL MENINGITIS.

Definition.—An acute infectious disease caused by the meningococcus and characterized by the production of purulent meningitis.

Synonyms.—*Epidemic cerebrospinal meningitis,* which is not a good term because the disease frequently occurs sporadically; *meningococcus meningitis,* which is a good term; *cerebrospinal fever,* which is preferred by many because indicating a disease entity, aside from any anatomical localization, and yet emphasizing the usual type of the disease; *spotted fever, petechial fever* and *malignant purpuric fever* are objectionable because emphasizing an unusual symptom. French, *meningite cerebrospinale epidemique.* German, *Epidemische Genickstarre.*

History.—Meningococcus meningitis is doubtless a disease of antiquity, but the first record of an epidemic of meningitis is that of Vieusseaux, who described a small outbreak occurring in Geneva in the winter and spring of 1805. In 1806, Danielson and Mann described an epidemic in Medfield, Mass., with 5 necropsies, and the Massachusetts Medical Society appointed a commission of James Jackson, Thomas Welch and J. C. Warren to investigate it. Since then hundreds of epidemics have occurred throughout the world and particularly in the United States, the great epidemics in New York City in 1904–1905 with 6755 cases and 3455 deaths, in Texas, during 1911–1912[1] and in the army during the World War, being especially noteworthy.

THE ETIOLOGY OF CEREBROSPINAL MENINGITIS.

In 1887, Weichselbaum, of Vienna, first described the Diplococcus intracellularis meningitidis as the cause of the disease and the organism has since become better known as the meningococcus. His discovery was discounted for many years because of confusion with the pneumococcus and staphylococcus, but the investigations of Councilman, Mallory, and Wright in the Boston epidemic of 1897 and of Bettencourt and Franca, in 1901–1903, firmly established its correctness. Furthermore, the disease has been produced experimentally in rabbits, dogs and monkeys by subarachanoid injection of pure cultures and even by intravenous inoculation when the resistance of the meninges has been reduced by intraspinal injections of normal serum, and the

[1] For an excellent review of this epidemic consult Sophian (Epidemic Cerebrospinal spinal Meningitis, St. Louis, C. V. Mosby, 1913.

uniformity with which the diplococci are found in the cerebrospinal fluid leaves no reasonable doubt of its etiological relationship to the disease.

The meningococcus is a small Gram-negative diplococcus closely resembling the gonococcus in stained smears. Tetrads are sometimes seen, but chains are unusual. The diplococci are commonly, but by no means uniformly, found within polymorphonuclear leukocytes; the preponderance of extracellular organisms is taken as a bad sign, since phagocytosis is the chief mechanism of resistance and recovery.

The organism is easily killed and requires rich culture media containing serum, ascites fluid or blood for growth. It ferments glucose and maltose but not saccharose, and this, together with other cultural and morphological characteristics usually suffice for its differentiation from other Gram-negative diplococci.

My means of agglutination, complement-fixation and phagocytic reactions different immunological strains have been identified by various investigators since Dopter first described a variant in 1903 and gave it the unfortunate and confusing name of "para-meningococcus." Probably four types or groups can be recognized, but there are so many cross-relations and overlappings among them that a sharp classification is hardly possible. Thus Dopter has divided them in four types, consisting of meningococcus and para-meningococcus alpha, beta and gamma; Gordon differentiates into Types I, II, III and IV. Nicolle divides them into Group A, corresponding to Dopter's meningococcus and Gordon's I and III; B, corresponding to Dopter's para-meningococcus alpha and Gordon's II and IV; C, corresponding to Dopter's para-meningococcus beta; and D, corresponding to Dopter's para-meningococcus gamma. The American division of Amoss is into normal or regular, irregular and para strains. Serological classification is of considerable practical importance in relation to the differentiation of meningococcus from other Gram-negative cocci in the naso-pharynx and the polyvalency of antimeningococcus sera for the treatment of the disease. At the present time there is usually no attempt made to type meningococci or to treat the disease with monovalent sera; American sera are required to have a polyvalency sufficient to cover all strains ordinarily encountered.

The frequency with which the meningococcus is found in the naso-pharynx of patients and contacts leaves no doubt but that this is the portal of entry. While it was formerly believed that the organism reached the cerebral meninges along the lymphatics of the olfactory nerves, or through the sphenoid and ethmoid sinuses or by way of the Eustachian tube to the middle ear and thence along the sheath of the auditory nerve, it is now regarded as practically certain that in the majority of cases the organism enters the lymphatics of the naso-pharynx and thence the blood with localization in the meninges. Blood cultures are frequently positive in the early stage and, indeed, fulminant cases may perish from a true septicemia with little or no

evidences of meningitis. Furthermore, the organism may localize in other tissues like the endocardium and joints.

Suppuration is a characteristic change, probably due to the production of soluble or exogenous toxins and more particularly of endotoxins and aggressins, the latter having as their chief characteristic the prevention or retardation of phagocytosis.

While the disease frequently occurs in epidemics, yet sporadic cases are not unusual. Epidemics are usually due to a great enhancement of virulence of the organism by rapid transfer from person to person and especially in camps. Undoubtedly the disease is spread by droplet infection from carrier to carrier until finally a susceptible individual develops it. Not infrequently it is impossible to trace the source of infection, probably because "carriers" of the organism are far more numerous than cases of the disease. Doctors, nurses and other members of a family do not ordinarily contract the disease, although cultures of the naso-pharynx are apt to show the presence of the organisms. During the disease and for variable periods after recovery it may be found in the naso-pharynx and the carrier problem is always important and difficult in this as in other carrier states.

Under the circumstances it is to be expected that the highest incidence is observed during the winter and late spring, when "colds" have reduced local resistance of the naso-pharynx and droplet infection is particularly likely from coughing and sneezing in street cars, "movies" or other crowded places. For the same reason the incidence is higher in cities than in country districts and it has long been noted that the mobilization of troops in barracks gave rise to favorable conditions for spreading the disease among the inmates and the surrounding territory. This also accounts for its greater prevalence among males. Cold and damp weather, fatigue and overcrowding are, therefore, the most important factors as is usual with other droplet infections.

IMMUNITY TO CEREBROSPINAL MENINGITIS.

Fortunately the majority of human beings, and especially adults, appear to have a high natural immunity to the meningococcus unless the organism is of high virulence or local resistance of the naso-pharynx is broken down by catarrhal infections. The non-epidemic incidence is usually less than 25 cases per 100,000 of population per year, and outbreaks in cities do not usually go above five times this rate.

Children are undoubtedly more susceptible than adults, probably because the latter have had the opportunity of developing immunity as a result of numerous minor and unrecognized infections of the nose and throat. About one-half the cases occur in children under five years of age, and the disease is more fatal in infants than in older children. Adolescents, however, are not infrequently attacked and especially from sixteen to twenty-five years of age; aged individuals,

however, may contract the disease and during the past year we have seen 2 cases in persons over sixty years of age.

All races are susceptible, and in epidemics the incidence among negroes is apt to be higher than among whites, probably because of more unfavorable hygienic conditions.

Recovery from the disease appears to be largely due to the production of agglutinins, opsonins and bactericidal substances promoting phagocytosis of the cocci as well as their extracellular destruction.

THE PROPHYLAXIS OF CEREBROSPINAL MENINGITIS.

Fortunately meningococcus meningitis is not very infectious and secondary cases in households are unusual. But the patient should be isolated and visits from friends and relatives forbidden or reduced to a minimum. In the presence of an epidemic unnecessary contact among the public at large should be discouraged and the least necessary gatherings forbidden.

Bed-side prophylaxis is important in all cases on account of the danger of droplet infection. Intimate contact with the patient should be avoided. In a hospital ward, where other diseases are being treated, the beds should be spaced at least 8 feet apart and adequate ventilation maintained.

Physicians, nurses and others in attendance should especially avoid contact with the sneezings and coughings of the patient. It is advisable to wear a mask and cleansing of the throat with bland washes is to be recommended. The nose and throat discharges of the patient should be carefully collected and destroyed. The physician and nurses should carefully wash the hands and particularly avoid all undue exposure to cold and fatigue, which are important predisposing factors to infection. Nurses should not be kept on duty too long, and required to exercise a few hours daily in the open air.

In epidemics and particularly in the army the culturing of contacts and isolation of carriers has aided in checking the spread of the disease although an organization for the maintenance of the isolated carriers is required. Following recovery it is advisable to culture the naso-pharynx of the patient for meningococci and maintain quarantine until at least two or three consecutive negative cultures have been obtained. Otherwise the patient may be the means of creating new carriers, some of whom contract the disease. It is likewise advisable to culture the naso-pharynx of nurses and others in frequent contact with patients for the detection of carriers.

Vaccination Against Meningitis.—Sophian and Black[1] have shown experimentally that a polyvalent meningococcic vaccine, heated to 50° C., standardized in the usual manner, and given in three injections in doses of 100,000,000, 500,000,000 and 1,000,000,000, at intervals

[1] Jour. Am. Med. Assn., 1912, **49**, 527.

of a week, appears to afford a high degree of protection. In the blood serums of inoculated persons these observers were able to demonstrate opsonins, agglutinins and complement-fixing amboceptors. All evidence points to the efficacy of prophylactic vaccination, as only a moderate degree of immunity may give complete protection against the disease.

Black,[1] in a subsequent investigation, found the production of antibodies after vaccination and expressed the opinion that the immunity probably lasts for two years. Quarrelli[2] reports favorably upon this vaccination, and Whitmore, Fennel, and Petersen[3] vaccinated 55 persons with a lipovaccine and observed the production of agglutinins with moderate general reactions after large doses. Gates[4] administered polyvalent saline vaccine to 3700 volunteers in three subcutaneous injections at weekly intervals of 2,000,000,000, 4,000,000,000 and 4,000,000,000 or 8,000,000,000 cocci. These doses rarely caused more than the mildest local and general reactions, although exceptionally a more severe reaction with symptoms of meningeal irritation were observed. Specific meningococcus agglutinins were demonstrable in the blood serum of the vaccinated individuals.

It would appear, therefore, that immunization with polyvalent saline vaccines of meningococci in three doses by subcutaneous injection at weekly intervals may prove of value as aiding in the prophylaxis of meningococcus meningitis and especially when the disease occurs in epidemic form.

Serum Prophylaxis of Meningitis.—Passive immunization by means of the subcutaneous injection of antimeningitic serum was advised by Jochmann in 1906, but has not come into general use. The immunity resulting from injection of from 10 to 20 cc. of serum is only temporary, and probably lasts about a month. Another drawback is the resulting serum sensitization, which renders subsequent injections of serum more likely to be followed by serum sickness. In the presence of an active epidemic, such as that which occurred in Texas during 1912, immediate passive immunization of physicians, nurses and attendants by the subcutaneous injection of 15 cc. of serum, followed by active immunization with three doses of vaccine (500,000,000, 1,000,000,000 and 1,000,000,000) at intervals of a week, may be advisable. While there are no available statistics to prove the value of this procedure, it is, at least, a rational one, and since there is danger of contracting the disease, especially after prolonged contact, physicians should practice immunization during epidemics of this dreaded disease. In mixed passive and active immunization the serum probably affords immediate protection, and tides over any temporary negative phase or period of lowered resistance following the injections of vaccine.

[1] Jour. Am. Med. Assn., 1913, **50**, 1289; 1914, **53**, 2126.
[2] Policlinico, 1917, **24**, 501.
[3] Jour. Am. Med. Assn., 1918, **70**, 427.
[4] Jour. Exper. Med., 1918, **28**, 449.

PERIOD OF INCUBATION OF CEREBROSPINAL MENINGITIS.

The period of incubation in meningococcus meningitis is ordinarily stated to be from one to five days, but may be as long as nine to ten days, depending upon the virulence of the organism and susceptibility of the host. The mere presence of the meningococcus in the nasopharynx does not constitute infection. But when it has succeeded in reaching the deeper tissues and blood, infection has occurred and but twenty-four hours to a few days are ordinarily required for the production of symptoms of septicemia or meningitis.

THE SYMPTOMATOLOGY OF CEREBROSPINAL MENINGITIS.

Meningococcus meningitis usually (about 75 per cent of cases) begins *suddenly*. In some instances there is a prodromal period of malaise with sore throat or cold in the head, but it is doubtful if these catarrhal changes are caused by the meningococcus, although they undoubtedly favor infection with it. According to the virulence of the organism the disease varies considerably in both its onset and subsequent course and may be divided into several forms as follows:

1. **Fulminating or Malignant Form.**—In this form of the disease, so apt to be seen at the beginning of an epidemic, the attack is usually ushered in by chills and intense headache, sometimes accompanied by vomiting. Delirium follows in a few hours and the patient may become violent and even maniacal. Coma eventually supervenes in all cases, and the patient is apt to die in forty-eight hours or less of the onset. In some cases coma follows almost immediately; individuals have gone to bed apparently in good health, and have been found unconscious or even dead on the following morning. A purpuric rash is usually present, the blotches (vibices) varying in size from that of a pea to that of a plum. The temperature is usually increased, but may be subnormal; the pulse is feeble and fluttering and respirations rapid and shallow. Neck rigidity is usually slight or absent. The spinal fluid is usually negative but blood cultures are apt to be positive and the symptoms due to a septicemia rather than to a meningitis.

2. **Ordinary Form.**—In this form the disease is usually ushered in by complaints of sudden chilliness or shivering and definite rigors may occur. These are quickly succeeded by severe and throbbing frontal or vertical headache which soon increases in severity. There is usually complete loss of appetite, and a few hours later the patient may have repeated attacks of explosive *vomiting* but frequently without nausea. Persistent vomiting is a bad sign and is a constant symptom of posterior basic meningitis of infants. Constipation is usual but diarrhea sometimes occurs and especially in children.

The temperature is high (102° to 104° F.) and the pulse rapid. The mind is usually clear, although rambling incoherence and emotionalism are not unusual; as a rule, delirium soon makes its appearance in adult

cases and is usually succeeded by a stupor during which the patient shows considerable irritability. Finally, should the case fail to respond to treatment coma supervenes and remains until death. In infants and young children the disease is often ushered in by a convulsion; vomiting is less frequent but hyperesthesia is apt to be an early and prominent symptom, the child crying or screaming on being disturbed.

All of these symptoms are caused by a rise in intracranial pressure due to sudden increase of cerebrospinal fluid following the arrival of the meningococcus in the pia arachanoid; the spinal fluid is usually cloudy, but blood cultures are apt to be sterile.

Or the disease may have a *gradual onset* (about 20 per cent of cases) with increasing headache and pain and stiffness of the legs; backache may occur and likewise vomiting. Insomnia and loss of appetite are usually well marked, and may be accompanied by soreness of the throat and nose-bleed. Such symptoms may be present for several days before the patient is confined to bed and easily give rise to errors of diagnosis in sporadic cases because meningitis may not be suspected. We have seen cases of this kind more especially in adults. When meningitis is well developed *headache* is always a constant symptom and is apt to be more or less general; occasionally it is so severe as to cause the patient to scream with agony and may be associated with pain at the nape of the neck. Unfortunately it may not cease even in delirium, although relief probably occurs as the patient sinks into a comatose state. *Insomnia* is usually a troublesome feature due to severe headache and meningeal irritation.

The patient is usually irritable and hyperesthetic, resents being turned on his back, is apt to complain of feeling cold and prefers lying on his side, with the limbs in an attitude of flexion, with head thrown back and covered with bed clothes to shut out both light and noise. He looks profoundly ill and usually has an anxious expression, the face is apt to be flushed and the conjunctivæ hyperemic, although from time to time a certain amount of pallor is noticeable.

In young children the anterior fontanelle is often found tense and bulging in the early stage due to the presence of generalized hydrocephalus, and made more pronounced by crying; even the cranial sutures may show some separation. During the third week, however, the fontanelle may become depressed, even in cases terminating fatally. In adolescents and children with closed fontanelles, a moderate amount of hydrocephalus may be demonstrated by means of Macewan's percussion sign when a dull tympanitic note is elicited over the frontoparietal region.

By reason of involvement of the posterior nerve roots of the spinal cord or possibly of the anterior horn cells *muscular rigidity* and *altered reflexes* occur in all but the fulminant cases, perishing too quickly for their development. *Rigidity of the muscles of the neck* is a particularly characteristic and early sign, and as it progresses the head is retracted backward in order to reduce tension as much as possible and disappear-

ing gradually with recovery but suddenly with the onset of coma and death. *Rigidity of the spinal muscles* is also characteristic and in children this may develop into an *opisthotonus* in an effort on the part of the patient to relieve pressure and tension. The legs are also apt to be rigid. Muscle tremors may occur and generalized convulsions are common in infants and young children, but rare in adults except in epileptics when attacks may occur.

In patients over two years of age *Kernig's sign* is usually present when the meningitis has become well developed; Brudzinski's sign is likewise usually present. In a considerable number of cases there is loss of control of the sphincters. *Floccitation* (picking movements) and *carphology* (a movement of the hand in front of the face as if gathering imaginary objects) are sometimes seen in acute cases and are of grave import. The *pupils* are usually dilated and respond sluggishly to light; occasionally they are contracted. Optic neuritis is uncommon. *Strabismus* is frequently observed but not nearly as

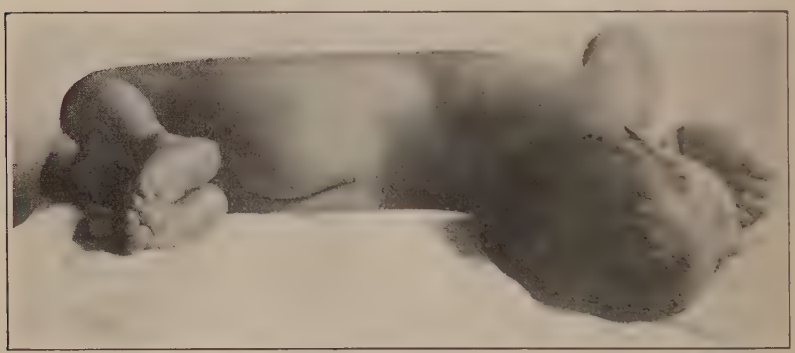


FIG. 153.—Extreme opisthotonus in cerebrospinal meningitis.

constantly as in tuberculous meningitis; nystagmus and ptosis sometimes occur; photophobia is frequently present in association with excruciating headache.

Instability of the vasomotor system is observed in almost all cases. *Tâche cérébrale* is invariably well marked, but is of no diagnostic value, as it is by no means confined to cerebrospinal meningitis. Alternate flushing and pallor is sometimes observed.

Contrary to general impressions, the *rash* in cerebrospinal meningitis is an extremely variable feature. In many cases no rash ever appears. Mottled erythemas of a transient nature may occur at almost any stage of the disease, but the true rash when present may be in the form of a maculo-papular eruption appearing within the first four or five days of illness and fading rapidly. Petechial and purpuric rashes, however, are more typical of the disease and usually occur in severe infections with meningococcus septicemia. The blotches are especially apt to be found at points of pressure about the knees, elbows and

shoulders. They are sometimes present on the first day of illness and seldom appear later than the third day.

Herpes appears in from 20 to 40 per cent of cases on the third to the seventh days after the onset of the disease. In many cases the margins of the lips only are affected, but in others the eruption spreads to the face, involving the chin, cheeks and nose, and not infrequently spreading even into the mouth and ears.

The *temperature* is variable and much modified by lumbar puncture and serum treatment. In fulminant cases it may not be present at all and, indeed, may be subnormal. In the average case it fluctuates between 100° to 104° F., but is very irregular and apt to terminate by lysis. Cases are not uncommonly met with, however, which exhibit a distinct crisis, in some instances both as regards the pyrexia and the symptoms and especially in abortive cases. Pyrexia persisting after the termination of meningitis is usually due to hydrocephalus or some

FIG. 154.—Great emaciation in cerebrospinal meningitis.

late complication like arthropathy, pyelitis, etc. Furthermore, a sudden rise of temperature is sometimes due to serum sickness, although an acute exacerbation or recrudescence of the infection is usually feared. Toward death in acute cases the temperature sometimes rapidly rises to 106° or 107° F.

The *pulse* is likewise variable and shows little or no relation to fluctuations in temperature. Very slow pulse-rates are not uncommon and have been ascribed to inhibition produced by action on the centers of the vagus nerve. Dicrotism is sometimes observed during or after the first week and in cases developing internal hydrocephalus the pulse usually becomes very rapid and feeble.

Respiration likewise bears but little relation to the pulse-rate and fever. In the majority of cases it is but slightly quickened. Cheyne-Stokes or Biot's respiration may be observed late in the disease and are of bad prognostic import. An undulatory type of breathing is not

infrequently seen in association with hydrocephalus. Death not infrequently occurs from sudden respiratory failure, the heart continuing to beat for an appreciable period after respiration has ceased. It probably results from some interference with the circulation to the fourth ventricle.

Wasting occurs in all but the mildest cases and independently of vomiting and diarrhea because of a disturbance of the normal trophic influences originating in the central nervous system. For the same reason *bed-sores* are also very liable to occur not only on the back and hips but also on other points of pressure, such as the outer sides of the knees, malleoli and elbows unless special precautions are taken.

3. **Abortive Form.**—Fortunately abortive cases are sometimes encountered characterized by the fact that in spite of an acute onset, chills, headache and vomiting, the symptoms subside almost as rapidly as they appear, the patient being convalescent within three or four days. Rigidity of the neck and Kernig's sign are almost always present, but a rash is very uncommonly seen. The spinal fluid is often clear to the eye, but a few pus cells and cocci are apt to be found upon microscopic examination.

4. **Chronic Forms.**—Since the introduction of antimeningococcus serum it is relatively uncommon to see the chronic form of cerebrospinal meningitis of former days usually occurring in untreated cases or those coming under treatment late in the disease. They are characterized chiefly by a protracted and lingering course, slow but steady deterioration, irregular temperature, rigidity of the neck, positive Kernig's sign, emaciation, incontinence of urine and feces and other signs of a gradually increasing intracranial pressure due to hydrocephalus. It may last for weeks and months.

A special chronic form is the *posterior basic meningitis* of children of a few months to three years of age. The onset and early course of the disease are similar to that of the ordinary form described above, but as it progresses the mental condition becomes one of extreme lethargy, the patient lying quite motionless with open and staring eyes and interrupted by an occasional cry. Head retraction and opisthotonus are usually prominent features as well as extreme extension of the limbs, periodical and persistent vomiting and progressive emaciation. Bulging of the anterior fontanelle is common and blindness of central origin not infrequent; spinal puncture not infrequently yields a "dry tap" due to the development of internal hydrocephalus.

5. **Recrudescent and Relapsing Forms.**—Sometimes the disease does not exhibit a uniform advance, but following a "crisis" lasting several days the fever and symptoms recur and the course of the disease is interrupted by one or more such "crises." This constitutes the *recrudescent form of meningitis*, but the presence of neck rigidity and of Kernig's sign indicate a persistence of infection and serve to differentiate it from a true relapse, even though the spinal fluid may be apparently clear and free of meningococci during the remissions.

This may go on for several weeks or even months, and when death occurs it is generally due to the development of hydrocephalus.

When, however, the patient has been free of all symptoms and signs, including Kernig's sign, along with a normal spinal fluid over a period of ten days to two weeks and then develops acute symptoms a true *relapse* may be said to occur. Fortunately they are rare, but evidently are due to lurking meningococci stimulated into renewed activity.

THE COMPLICATIONS AND SEQUELÆ OF CEREBROSPINAL MENINGITIS.

The complications of meningococcus meningitis are divisible into two main groups, namely: (*a*) Those resulting from the direct infection of the cerebral meninges with extensions along the cranial nerves; (*b*) those produced by true septicemia or blood-stream infections. On the whole, they are most likely to develop in the severe cases, although mild cases are by no means immune. Furthermore, they are much less frequently encountered than formerly, thanks to earlier diagnosis and specific serum therapy.

Hydrocephalus is certainly to be ranked among the most important complications. A *generalized form* may be seen due to a greatly increased amount of cerebrospinal fluid throughout the subarachanoid space, both in the ventricles and externally, and without obstruction of the foramina of Magendie and Luschka. The symptoms are practically those of a mild internal hydrocephalus with headache, lethargy, vomiting, dilated pupils, etc., and an enormous increase of spinal fluid. As a general rule spinal puncture affords prompt relief, but it may be necessary to repeat it every twelve hours before permanent relief is secured.

Internal hydrocephalus is more frequent and more dangerous. It is due to complete or partial blocking of the foramina of Magendie and Luschka with accumulation of fluid in the ventricles. As a result the heavy cerebral hemispheres are apt to press down on the medulla and still further obliterate the foramen of Magendie. The onset is sometimes quite sudden but is far more frequently insidious and usually occurs in cases that have become subacute or chronic.

The general signs of meningitis, as neck rigidity, Kernig's sign and muscular rigidity, are usually present. Persistent vomiting may occur. The patient becomes progressively more tremulous with increasing lethargy and periods of low muttering delirium. Children show a progressive loss of interest in their surroundings, lying quietly for hours with a peculiarly vacant stare; in extreme cases they may give the purposeless and high-pitched anxious cry which is apparently automatic, independent of pain and called the "hydrocephalic cry." In most cases there is incontinence of feces and urine, progressive wasting, bulging of the anterior fontanelle in infants, irregular temperature, weak and rapid pulse, marked dilatation of pupils with occasional

blindness of central origin, etc.; death is usually due to respiratory failure. The cerebrospinal fluid obtained on daily puncture steadily diminishes until often none can be withdrawn.

Pneumonia is another dreaded complication because it is usually fatal and may occur in as high as 10 per cent of cases.

Bronchitis is fairly common as likewise *rhinitis* and *sinusitis*, especially of the sphenoidal and ethmoidal cells. *Pleurisy* generally accompanies the pneumonia.

Pericarditis occurs only in acutely fatal attacks and *ulcerative endocarditis* is distinctly rare. Cloudy swelling of the heart muscle with some dilatation is not uncommon.

Arthritis is also frequent, being encountered in 10 to 15 per cent of cases and evidently due to blood infection.

Pyelitis has been encountered and especially in certain epidemics, notably the Texas epidemic. The *kidneys*, however, are frequently involved. Polyuria is not uncommon early in the disease and albuminuria has been observed in as high as 40 to 50 per cent of cases. Glycosuria is rare but hematuria may be seen and meningococci have been recovered from the urine by various investigators.

The *eyes* may be involved by conjunctivitis and keratitis. Optic neuritis may follow involvement of the nerve by inflammatory exudates at the base of the brain. Acute papillitis has occurred as well as purulent choroido-iritis. Paralysis of some of the external muscles may be seen.

The *ears* may be involved. Temporary or permanent deafness may result from extension of the exudate along the sheath of the auditory nerve into the internal auditory canal, resulting in both the seventh and eighth nerves becoming imbedded in pus, although the facial nerve being more compact is not nearly so apt to show paralysis as is the auditory. Acute labyrinthitis, otitis media and mastoiditis are sometimes seen and especially in acute infections.

McLean and Caffey[1] have recently reported that of 44 infants, ranging in age from thirty-five days to four and a half years, who had meningitis from one to ten days previously, 9 showed sequelæ as follows: 4 deaf-mutism, 2 hydrocephalus, 2 visual impairment and 1 mental deficiency.

Spinal Fluid Changes.—The normal cerebrospinal fluid is under a pressure of 2 to 8 mm. of mercury with the patient lying perfectly quiet on the side, is water clear, shows 0 to 8 cells per c.mm., contains about 0.03 per cent protein, which gives a negative Pandy and other ordinary protein reactions and a trace of glucose. It is sterile if collected aseptically and gives no precipitation of colloidal gold or mastic.

In meningitis the changes vary with the severity of the disease. During the early stage of meningococcus septicemia it shows no changes at all, but upon localization of the organisms in the meninges alterations soon take place.

[1] Jour. Am. Med. Assn., 1927, **87**, 91.

The *pressure is usually increased* probably because of hyperemia of the choroid plexuses as well as of the pial vessels with increased secretion of cerebrospinal fluid and serous exudation. The amount of pressure varies with the increase in amount of fluid and the freedom of passage from the ventricles to the spinal subarachanoid space. With a gauge No. 19 needle the rate of flow under normal conditions is from 5 to 10 drops per minute, but in meningitis it is apt to spurt from the needle until the fluid thickens with pus cells when it flows very slowly and, indeed, may become too thick to flow at all unless a much larger needle is used.

The *appearance is changed* from water clearness to opalescence on up to turbidity and pure pus. Blood may be present. In the earliest stage the fluid may be quite clear as likewise in internal hydrocephalus and other chronic forms, although meningococci may be found in culture. In cases of meningeal hemorrhage the fluid may become yellowish in color (xanthochromia) and may coagulate upon standing (syndrome of Froin).

The total cells are increased up to hundreds and thousands per cubic millimeter. Smears show a great preponderance of polymorphonuclear leukocytes.

The protein is increased with strongly positive Nonne-Apelt, Ross-Jones, Pandy, Noguchi and other simple qualitative tests.

Sugar is usually absent or greatly reduced, and the fluid fails to reduce Fehling's or Benedict's solutions, probably because the glucose is hydrolyzed by the meningococcus.

The chlorides are apt to be slightly reduced, the normal chlorides varying from 675 to 750 mg. per 100 cc. of fluid.

As recovery takes place sugar reappears in the fluid and its persistent absence is of bad prognostic import, probably because it indicates the continued presence of meningococci.

Smears usually show Gram-negative diplococci, intracellularly and extracellularly, typical preparations looking for all the world like smears of pus in gonorrheal urethritis. *In the early stage, however, the organisms are usually very scanty* and prolonged search may be required; indeed, none at all may be found in the first fluid, although *cultures may be positive* when 1 cc. or more of fluid is planted on blood or serum agar.

Colloidal gold and mastic tests usually show meningitic curves of precipitation. The fluid may also contain precipitins and agglutinins for meningococci and yield positive complement-fixation reactions with meningococcus antigen.

As recovery takes place the meningococci are found more and more intracellularly and finally disappear in smears and cultures. *The appearance of the fluid, however, may continue very cloudy, due to the presence of leukocytes resulting from aseptic irritation of the meninges by injections of serum.* The pressure subsides, sugar appears and the proteins decrease.

Blood Changes.—A *leukocytosis* occurs in the majority of cases with an increase of the polymorphonuclear cells. Acute fulminating cases succumbing within forty-eight hours have shown leukopenia evidently due to severe infection. Otherwise, however, the blood changes usually bear a relation to the severity of the disease but are not in any manner characteristic since polynuclear leukocytosis is found in other meningitides.

In 1899 Gynn[1] first reported the presence of the meningococcus in the blood in meningitis, and since then numerous investigators have shown that *early* blood cultures may yield positive results in severe infections. Thus Elser and Huntoon,[2] using an ascitic broth dilution method (transplanting to ascitic agar plates), obtained 27 per cent positive cultures in 41 cases, but concluded that these were instances of a transient invasion of the blood rather than of a true proliferating septicemia. During the epidemic in 1918 Baeslack and his colleagues[3] reported 36 per cent and Herrick[4] as high as 80 per cent positive cultures. Maxcy,[5] however, using a similar technique, found only 1 case with a positive blood culture preceding positive spinal cultures out of 27 clinically suggestive patients. It may well be, therefore, that with improved technique the septicemic stage can be proven for the ordinary non-fulminating case, and especially when two or more cultures are made, but under routine conditions probably not more than 25 per cent of cases will yield positive results, and then only in the more severe infections. When meningitis is well developed blood cultures are usually sterile unless severe complications are present.

THE PATHOLOGICAL ANATOMY OF CEREBROSPINAL MENINGITIS.

The earliest anatomical change is a hyperemia and infiltration with polymorphonuclear leukocytes of the pia and arachanoid over the brain and spinal cord. Pus is then produced which is most prominent along sulci and around vessels and especially at the base of the brain and the posterior surface of the cord, but usually extending up around the lateral surfaces of the cerebrum, sparing in general the longitudinal fissure, but abundant over the upper surface of the cerebellum. Collections are usually found at the roots of the cranial and spinal nerves. In untreated and chronic cases these exudates are apt to become organized into adhesions and thickened meninges.

The cells of the exudate are largely polymorphonuclear leukocytes, but lymphoid and plasma cells may be found in the tissues toward the periphery of infiltrations, and very large cytophagocytic cells are also found which, according to Councilman, Mallory, and Wright, originate from connective tissue cells or from cells lining the lymph spaces. The

[1] Bull. Johns Hopkins Hosp., 1899, **10**, 112.
[2] Jour. Med. Res., 1909, **15**, 369.
[3] Jour. Am. Med. Assn., 1918, **60**, 684.
[4] Ibid., **61**, 612.
[5] Jour. Infect. Dis., 1918, **23**, 470.

proliferative endarteritis, common in tuberculous and pneumococcus meningitis, is unusual in this disease.

The ventricles of the brain also participate in the process, and if pus or adhesions have occluded the foramina of Magendie and Luschka, obstructive hydrocephalus results; if the cerebral meninges are blocked off by adhesions surrounding the foramen magnum the ventricles may become dilated (communicating hydrocephalus).

The meningeal changes may extend into the cortex of the brain but less often into the spinal cord. Hemorrhages may occur into the nerve tissue and areas of softening coincide with paralyses. The cranial and spinal nerve roots are apt to show inflammation and infiltration.

Other pathological changes are similar to those found in acute infectious diseases, as enlargement of the spleen, bronchitis with foci of bronchopneumonia, cloudy swelling of the heart sometimes associated with purulent pericarditis, petechial hemorrhages in the gastrointestinal mucosa, cloudy swelling of the kidneys, etc.

THE DIAGNOSIS OF CEREBROSPINAL MENINGITIS.

The keynote in diagnosis is examination of the cerebrospinal fluid.

The tubercle bacillus, pneumococcus, streptococcus and influenza bacillus may also produce meningitis with signs and symptoms closely resembling those produced by the meningococcus, but spinal puncture and examination of the fluid generally suffices for differential diagnosis. Pneumococcus and streptococcus meningitis usually have their origin in preliminary infections of the ear, mastoid cells or nasal accessory sinuses, while meningococcus meningitis generally develops without these well-defined primary foci; the same is true, however, in tuberculous and influenzal meningitis.

Influenza may be particularly confusing and in this disease, as likewise in pneumonia, typhoid fever, typhus fever, septicemia, acute rheumatic fever, measles, whooping cough, tetanus and even in gastroenteritis of children there may be well-defined symptoms due to acute meningeal congestion, so well known as *meningismus* or *"serous meningitis;"* the same sometimes occurs in acute alcoholism, uremia, diabetic coma and lead poisoning, but examination of the spinal fluid usually serves for differential diagnosis according to the table on p. 842.

Acute anterior poliomyelitis may likewise require exclusion and we have known several cases of meningococcus meningitis in women diagnosed as hysteria until the spinal fluid was examined.

Localized infections as localized meningitis of otitic or mastoid origin, cerebral abscess and later sinus thrombosis may present difficulties in differential diagnosis until spinal puncture and examination of the fluid have been made.

Changes.	Acute suppurative meningitis.				Tuberculous meningitis.	Meningismus.	Poliomyelitis.
	Meningococcic.	Pneumococcic.	Streptococcic.	Influenzal.			
Pressure	Greatly increased	Greatly increased	Greatly increased	Greatly increased	Greatly increased	Greatly increased	Slightly increased.
Appearance	Cloudy	Cloudy	Cloudy	Cloudy	Clear	Clear	Clear or opalescent.
Total cells	Hundreds to thousands	Hundreds to thousands	Hundreds to thousands	Hundreds to thousands	Few hundred	About normal	20 to few hundred.
Kind of cells	Polymorphonuclears	Polymorphonuclears	Polymorphonuclears	Polymorphonuclears	Small lymphocytes	Lymphocytes and endothelium	Small lymphocytes.
Protein	Greatly increased	Greatly increased	Greatly increased	Greatly increased	Greatly increased	Not increased	Slightly increased in about 30 per cent.
Sugar	None	None	None	None	Present, but reduced	Present	Present.
Chlorides	Slightly reduced	Slightly reduced	Slightly reduced	Slightly reduced	Greatly reduced	Normal	Normal.
Smear	Gram-negative diplococci	Gram-positive diplococci and short chains	Gram-positive cocci in chains	Gram-negative bacilli	Acid-fast bacilli	None	No organisms.
Culture	Meningococci	Pneumococci; inulin fermentation; bile-soluble	Streptococci; hemolytic; inulin not fermented; not bile-soluble	Influenza bacilli	No growth for weeks; positive guinea-pig inoculation	Sterile	Sterile.

THE PROGNOSIS OF CEREBROSPINAL MENINGITIS.

The *mortality* in cerebrospinal meningitis varies according to the virulence of the organism, the resistance of the patient and to the duration of the disease before diagnosis and the institution of specific serum therapy. It is always apt to be higher in epidemics than in sporadic cases because of a higher virulence of the organism.

Prior to the introduction of serum in treatment the mortality in epidemics varied from 30 to 100 per cent with a general average of about 70 per cent. Since 1910 it has varied from about 6 to 66 per cent with a general average of about 28 per cent.

But under proper conditions it is still less, that is to say, under conditions of early diagnosis and the prompt institution of serum therapy. Thus when serum was given during the first three days the mortality in epidemics has been about 18 per cent and 27.2 and 36.5 per cent respectively when instituted on from the fourth to seventh and after the seventh days.

Age also has an influence, the mortality being particularly high in nurslings under a year as indicated in the following table from Neal:

Age.	Cases.	Mortality, per cent.
Under 1 year	102	46.0
1 to 2 years	46	31.0
2 to 5 "	89	16.8
5 to 10 "	108	25.9
10 to 20 "	84	23.8
Over 20 "	80	31.0

In sporadic cases the mortality is usually lower and as more physicians are trained in the technique of spinal puncture and intraspinal serum therapy it may be confidently expected that lower mortality-rates will prevail in the future.

Death may be due in the early fatal cases to cardiac failure, although respiratory failure is the usual cause. Blood-pressures consistently below 120 mm. in the first sixty hours, or about 120 mm. thereafter, are said to be of serious import. Complications, and particularly pneumonia, are sometimes responsible for death. In chronic cases death is generally caused by hydrocephalus and the extreme wasting due to central trophic disturbances.

The promptness with which specific serum is administered also influences the duration of the disease and the incidence of *complications and sequelæ*. Cerebrospinal fever is a treacherous disease, since it may kill within a few days, although patients surviving the first three or four days are apt to recover under efficient serum therapy. So much depends upon the thoroughness and promptness of serum therapy that figures as to the length of the convalescence are of little value; it may be stated, however, that early and efficient serum treatment has very materially shortened the course of the disease. The same is true of the complications and sequelæ which have been materially reduced, and especially the eye and ear complications.

THE TECHNIQUE OF SPINAL PUNCTURE AND INTRASPINAL INJECTION.

Therefore, the most important procedure for early diagnosis and proper treatment in cerebrospinal meningitis is spinal puncture and intraspinal injections of specific serum. In the presence of an epidemic, puncture should be done with less indications than in sporadic infections, but in all cases it should be performed on serious suspicion as soon as possible, with antimeningitis serum on hand for administration if a cloudy fluid is obtained. It is true that exceptional cases of meningitis may be due to streptococci, pneumococci, influenza or tubercle bacilli, but the injection of antimeningococcus serum into these will do no harm even though it may do no good.

In adults puncture may be delayed if the symptoms are mild and likely due to meningismus, but it is a mistake to delay too long. Under proper conditions it never does any harm and may do good in the way of relieving pressure in meningismus or poliomyelitis, even though a true meningitis is absent. In nurslings the absence of localizing signs is particularly apt to be misleading but convulsions, irregular fever, restlessness, twitching and regurgitation not preceded by feeding, constitute a train of symptoms justifying spinal puncture.

Indeed there are no real contraindications when puncture is done by one experienced in the little operation. Secondary infection of the meninges is so rare as scarcely to merit comment. And the danger of spinal puncture favoring infection of the meninges when bacteria are present in the blood has been greatly overemphasized. In our experience and opinion this does not occur with spinal puncture and the slow removal of spinal fluid, although the results of our animal experiments have indicated that the possibility exists when the meninges are injured by the injection of normal serum or some other irritant.

Technique of Spinal Puncture.—As a general rule, the *needles* furnished with packages of antimeningitis serum are satisfactory. In the early stages of the disease, when the fluid flows freely, it may be of gauge No. 19 but later on gauge No. 15 is indicated when the fluid is more purulent. The needle should be very sharp, with a short bevel and *should fit the gravity outfit or syringe if serum is to be given.*

The patient should be placed on his side with knees drawn up as far as possible, as shown in Figs. 155 and 156; this is sometimes very difficult and painful and a few drops of chloroform may be required for relaxation of the spastic muscles. When adults greatly fear the puncture the skin and subcutaneous tissues may be anesthesized with injections of sterile 1 per cent solutions of novocaine or butyn, but this is not ordinarily required in meningitis.

The skin of the back should be prepared by the application of one or two coats of tincture of iodine. The physician's hands should be properly cleansed or sterile rubber gloves worn.

Puncture should be made in the median line in the "soft spot" between the spinous processes of third and fourth or fourth and fifth lumbar vertebræ. The lateral route may be used, but we believe the former to be easier and better. The needle should be entered

FIG. 155.—Proper arrangement for spinal puncture in meningitis. The back is well arched and perpendicular to the table. (Kolmer: Chemotherapy and the Treatment of Syphilis, W. B. Saunders Company.)

slowly and gently rather than by a sudden thrust; the patient must be kept quiet, in order not to break off the needle by sudden twists or turning over on the back. As the needle reaches the subarachanoid space there is a characteristic "give away" sensation. If bone is struck the needle should be partly withdrawn and passed in a slightly

FIG. 156.—Improper arrangement for spinal puncture in meningitis. The back is not arched and has slumped forward. (Kolmer: Chemotherapy and the Treatment of Syphilis, W. B. Saunders Company.)

different direction, but if the patient is in good position and the needle passed strictly in the middle line puncture is usually successful even in the hands of those doing it for the first time. Clumsiness and brutality only are inexcusable.

The spinal fluid pressure may be measured as shown in Fig. 157 when it is desired to measure it accurately. Ordinarily this is not required for diagnosis, since the flow of fluid is generally in ratio to the pressure if the needle is not obstructed.

Fluid should be collected in sterile containers as test-tubes or bottles and sent *at once* to a laboratory for examination. The amount to remove depends upon circumstances. If under pressure, this should be at least 10 to 20 cc. or even more in order to reduce the pressure to about normal (5 to 10 drops per minute). If the fluid is perfectly

Fig. 157.—Measuring the spinal-fluid pressure. (Kolmer: Chemotherapy and the Treatment of Syphilis, W. B. Saunders Company.)

clear, the injection of serum may be delayed, but if opalescent or cloudy, antimeningitis serum may be injected at once, providing cloudiness is not due to a few drops of blood in the fluid which may readily give the impression of a cloudy fluid due to meningitis.

Dry taps may be due to the fact that the subarachanoid space has not been entered at all or to obstruction of the needle. In the latter merely rotating the needle or gently inserting the trocar suffices for correction. True dry taps may occur in advanced internal hydrocephalus when there is practically no fluid in the subarachanoid space.

At the close of the operation the iodine should be removed from the skin with alcohol, and the puncture wound sealed with flexible collodion and cotton or with gauze and adhesive straps. Since several punctures are generally required it is necessary to reduce irritation of the tissues to a minimum.

FIG. 158.—Outfit for the intraspinal injection of antimeningitis serum by gravity. (Kolmer: Infection, Immunity and Biologic Therapy, W. B. Saunders Company.)

Technique of Intraspinal Injection of Serum. Serum is now generally given by gravity, as it is safer than the older syringe method because if symptoms of collapse appear they may be relieved by allowing fluid to flow out into the container. The outfits furnished

by the manufacturers of serum are generally satisfactory (Fig. 158), but a good one can be improvised by using the barrel of a 20-cc. syringe, as shown in Fig. 159, attached to 12 to 14 inches of soft rubber tubing fitted with an adapter easily and tightly fitting the needle. Of course, the whole must be carefully sterilized beforehand.

If assistance is at hand it is good practice to take *blood-pressure readings* during the injection of serum, as a drop of 20 mm. or more is sometimes the first sign of collapse.

The serum should be first warmed by wrapping the vial in towels wrung out in hot water, as the injection of cold serum increases pain and the danger of collapse.

FIG. 159.—Apparatus for intraspinal injection by gravity. (Kolmer: Chemotherapy and the Treatment of Syphilis, W. B. Saunders Company.)

After withdrawing 10 to 30 cc. of fluid and even more if the pressure is high, but usually a little more than the amount of serum to be injected, the gravity outfit is attached and the serum *slowly* injected. As a general rule, some pain is produced and especially in the legs, due to pressure, but by gentleness and slow injection it is generally possible to give all of the serum. If signs of collapse appear the spinal canal may be drained a little into the gravity outfit and later reinjected. Atropine and caffeine may be given by subcutaneous injection, and it is well to have these on hand in case of immediate need.

Serum may also be given by *syringe* as shown in Fig. 160, and is sometimes required when it is necessary to give it under pressure in

thick plastic cases. Under these conditions it is sometimes advisable to insert a needle high up in the dorsal vertebræ or into the cisterna magna (technique described below) and wash out between the two needles with warm sterile saline solution before the injection of serum. Syringes are usually required.

There is usually a drop of temperature within four to eight hours due to the withdrawal of the purulent fluid, even though serum has not been given.

Pain and weakness in the back, so often complained of for some time after recovery from meningitis, are more likely to be sequelæ of the disease itself than due to repeated spinal punctures.

Fig. 160.—Intraspinal injection of serum by a syringe. (Kolmer: Infection, Immunity and Biologic Therapy, W. B. Saunders Company.)

Serum sickness follows in many cases and the physician should be perfectly familiar with the symptom and warn the family of its possible occurrence in order to allay fears of recrudescence of the meningitis.

Technique of Cisternal Puncture.—In exceptionally severe cases of meningitis it is sometimes advisable to inject serum into the cisterna magna, to which further reference will be made later on. The anatomical relations of the cisterna magna and general direction of the needle are shown in Fig. 161, as determined by Wegeforth, Ayer and Essick in a thorough investigation of this subject. The puncture is made through the skin, subcutaneous tissues and the occipito-atlantoid

ligament which stretches between the posterior rim of the foramen magnum to the corresponding position on the first cervical vertebra.

For introducing the needle a point is selected in the mid-line of the back of the neck just above the spine of the axis. The glabella and upper edge of the external auditory meatus are valuable for directing the course of the needle, for a line passing through them and the point of insertion on the back of the neck will pass also through the occipito-atlantoid ligament. In thin individuals palpation over the back of the neck often reveals a deep depression between the occipital protuberance and the spine of the axis, and with the tip of the finger

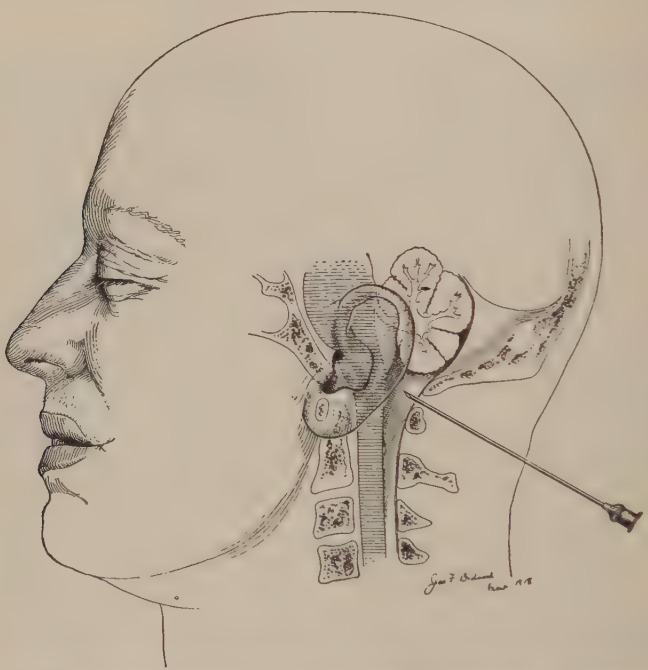


FIG. 161.—The landmarks used in performing cisternal puncture. (Kolmer: Chemotherapy and Treatment of Syphilis, W. B. Saunders Company.)

the approximate position of the ligament can be directly located. The distance for the needle to traverse is about 4 cm., rarely exceeding 5 cm. and never less than 3 cm. As in lumbar puncture, however, one must rely upon the tactile sense, the needle giving the same peculiar "give away" sensation when entering the cistern as when it enters the lumbar subarachanoid space.

Technique of Ventricular Puncture.—Drainage of the lateral ventricles and the injection of serum are likewise indicated in some cases. Various methods have been described for ventricular puncture, but the procedure is really a major operation, at least for the first puncture,

since a small trephine of the skull is required. Under ether anesthesia Hammond and Sharpe make an incision a little in front of the bregma and 2.5 cm. from the sagittal sinus and remove a 1.5-cm. button of bone. The dura is incised and a slender cannula with a blunt point is introduced at a point free from cortical vessels and passed downward and a little backward into the lateral ventricle. The head of the table is lowered and from 10 to 20 cc. of fluid collected. The table is now raised and the injection slowly given by gravity. In second and subsequent injections the scalp is infiltrated with novocaine and the puncture made without general anesthesia since the brain is not sensitive.

In infants the puncture and injection of serum may be made through the anterior fontanelle.

THE SERUM TREATMENT OF CEREBROSPINAL MENINGITIS.

During the pandemic of meningococcal cerebrospinal meningitis in 1904–1905 several laboratories sought to produce an immune serum for the purpose of treating human cases of this infection.

After pursuing experimental studies on the subject on the lower animals, Jochmann,[1] in 1905, immunized a horse and used the serum in the treatment of 38 cases of epidemic meningitis. At first he employed the subcutaneous method of injection, and later he used the intraspinal method. The results were quite encouraging, and during the following year 30 more cases were treated, with a resulting mortality of 27 per cent as against a mortality of 53 per cent in untreated cases.

At about the same time Kolle and Wassermann[2] reported that they had prepared an antimeningococcus serum, which had not, however, up to that time been used in the treatment of human infections. A year later serum was administered subcutaneously and then intraspinally, with encouraging results.

In this country Park had, in 1905, prepared an antimeningococcus serum, which was used in the treatment of 20 cases in Hartford, Conn., by subcutaneous injection, but without beneficial results. Jochmann had in the meantime shown the superiority of intraspinal injections, and this method soon supplanted the subcutaneous method.

In 1905, Flexner began a series of studies regarding experimental meningococcus infections in the lower animals and the therapeutic value of antimeningococcus serum. These valuable experiments attracted the attention of the world, and placed this method of treatment upon a firm basis. In 1906, Flexner[3] proved that a specific immune antimeningococcus serum could be produced that, if injected intraspinally, would save the lives of monkeys. Later horses were

[1] Deutsch. med. Wchnschr., 1906, **22**, 788.
[2] Ibid., vol. **32**, No. 16.
[3] Jour. Am. Med. Assn., 1906, **47**, 560.

immunized and the serum used in the treatment of human infections during an epidemic in Akron, Ohio, in May, 1907. In a short time the serum was used extensively in other epidemics, and a report of these early cases was made by Flexner[1] in 1907. A later report by Flexner and Jobling,[2] covering the treatment of 400 cases, showed that the mortality had been reduced from 75 per cent to below 30 per cent. In 1909 they reported[3] upon 712 cases treated with the serum, with a mortality of 31.4 per cent. In a subsequent report Flexner[4] reviewed all the cases, 1300 in number, gathered from all parts of the world, treated with serum prepared in the Rockefeller Institute. The general mortality-rate was given as 30.9 per cent, as against 75 to 80 per cent among cases not receiving serum treatment. Of 1394 cases treated with serum during the Texas epidemic by Sophian[5] (1912), the mortality-rate was 37 per cent, as compared with a mortality of 77 per cent among 562 cases receiving no serum.

Action of Antimeningococcus Serum.—Experiments *in vitro* show that a potent antimeningitic serum possesses three chief antibodies upon which its curative powers probably depend, namely: (1) *Bacteriotropins* (immune opsonins), which lower the resistance of the meningococci and facilitate their phagocytosis; (2) *bactericidins*, which kill the cocci extracellularly, either with or without final lysis; (3) *antitoxins*, which neutralize the true extracellular toxin, which some strains of meningococci apparently produce in varying degree, and *antiendotoxins*. In addition to these are the *agglutinins*, which probably aid in bacteriolysis, and *anti-aggressins*, which may assist in the process of phagocytosis.

Microscopic examination of a direct stained smear of the sediment of cerebrospinal fluid obtained from fresh cases will show large numbers of polymorphonuclear leukocytes and cocci, the majority of the latter being extracellular. As the case improves, whether under serum treatment or spontaneously, the microörganisms diminish in number and become intracellular, frequently appearing clumped and failing to grow in culture. It would appear, therefore, that a cure is brought about partly by means of phagocytosis aided by bacteriotropins; by bacteriolysis through the agency of specific bacteriolytic amboceptors in the immune serum and complements in the spinal fluid and blood serum, and to some extent by neutralization of a toxin with antitoxin.

A potent antimeningococcus serum furnishes these main antibodies, and since the first two must act locally upon the cocci infecting the meninges, the serum must be applied locally and directly by intraspinous and subdural injection, since only traces of immune serum could eventually find their way into the cerebrospinal fluid if the serum were injected subcutaneously or intravenously. On the other hand,

[1] Jour. Exper. Med., 1907, **9**, 168.
[2] Ibid., 1908, **10**, 141.
[3] Jour. Am. Med. Assn., 1909, **43**, 1443.
[4] Jour. Exper. Med., 1913, **17**, 553.
[5] Epidemic Cerebrospinal Meningitis. St. Louis, C. V. Mosby Company, 1913.

in the treatment of meningococcus bacteriemia and toxemia the serum should be injected intravenously and subcutaneously.

Polyvalent and Monovalent Sera.—Unfortunately, an immune serum may not contain the antibodies for the cocci producing a given infection, and hence the serum, even though it is skilfully administered in large doses, will have no influence upon the disease. Apparently the cocci of these resistant or "fast" strains are uninjured by the antibodies in the serum. To overcome this difficulty, a large number of different strains of meningococci are used in immunizing horses. In the Rockefeller Institute horses have been immunized with as many as 40 strains, and during the World War this serum yielded excellent results. If, however, the serum of one laboratory is found to exert no beneficial effect, the physician should use the serum of another, for different laboratories probably immunize their horses with cultures not in common use. *It is highly desirable to secure cultures of these "fast" strains. These should be sent at once to laboratories engaged in the production of antimeningitic serum, for the larger the number of these strains used in immunization, the more potent and valuable will be serum.* Very probably the use of monovalent sera will still further improve the results of the serum treatment of this disease.

Matsunami, Toyama, and Kolmer[1] have found that the addition of fresh sterile normal human serum to antimeningitis serum increases its opsonic and bactericidal properties and this procedure is worth trying in the treatment of serum-resistant cases, although the time and trouble involved prevents its general use; we believe, however, that in exceptional cases it is worth while adding 2 to 5 cc. of *fresh, sterile* serum to the dose of antimeningitis serum before injection.

Intraspinal Administration and Dosage of Antimeningitic Serum.—In Acute Meningitis.—As a rule, *serum should be injected into the spinal canal as early in the disease as possible, and in such maximum amount as is compatible with safety.* Intraspinal injection is absolutely necessary, for the serum must be brought into contact with the infected membranes, and only a trace would reach the spinal fluid if the serum were injected subcutaneously or intravenously.

As a rule, the amount of serum injected should be slightly less than the amount of fluid withdrawn. When the injection is controlled by the blood-pressure readings, the amount varies considerably, usually the injection should stop when the pressure falls another 10 or 15 mm. For adults the dose of serum should be about 30 cc.; for an infant, about 15 cc.

The serum should be allowed to flow in slowly, an ordinary injection consuming at least ten or fifteen minutes. If symptoms of collapse should appear before an adequate amount of serum has been injected, the funnel may be lowered and the spinal fluids allowed to flow out. When the symptoms have disappeared the injections may be continued and satisfactorily completed.

[1] Jour. Immunol., 1918, **3**, 157 and 177.

When the physician cannot administer the serum by the gravity method or under blood-pressure control, the injection may be given by means of a syringe. It should be given slowly, and the patient observed closely in order to detect the general symptoms of collapse. The amount of serum injected should not be larger than the amount of cerebrospinal fluid withdrawn. According to Sophian, the average doses are as follows

	Dose of antimeningitis serum, cc.	Amount of fluid withdrawn, cc.
1 to 5 years	3 to 12	12
5 to 10 "	5 to 15	15
10 to 15 "	10 to 20	20
15 to 20 "	15 to 25	30
20 years and over	20 to 30	40

The injection of too large a dose of serum may be followed by headache, pain in the back and legs and restlessness. When the amount of serum injected exceeds the amount of spinal fluid withdrawn the symptoms just named must be regarded as the signal to stop; otherwise they may be disregarded.

Intravenous Administration of Antimeningococcus Serum.—During epidemics of meningitis it may be possible to detect cases in the bacteriemic state when meningococci are present in the blood and clear fluid is collecting in the ventricles. In these and in all severe fulminant infections it is good practice to inject from 30 to 100 cc. of serum intramuscularly or intravenously. It is advisable to secure a culture of blood in ascites dextrose broth in all cases in adults and older children. If sufficient serum may be obtained and the expense is a secondary consideration, an intravenous or intramuscular injection, given at the outset and once or twice during the acute stage, may benefit the patient by neutralizing toxins and possibly prevent complications due to the entrance of meningococci into the blood stream. Furthermore, as shown by Flexner and Amoss,[1] in poliomyelitis the intraspinal injection of serum increases the permeability of the choroid plexus and meninges, permitting the passage of immunity principles from the blood into the cerebrospinal fluid. For this reason the intravenous or intramuscular injection of antimeningitis serum in conjunction with intraspinal injections may be particularly advantageous in the treatment of severe infections.

With intravenous injections of serum care must be exercised against severe reactions. It is good practice to first inject subcutaneously 1 cc. of the serum and give the balance about an hour later, injecting slowly. Blackfan[2] has directed particular attention to these reactions and advises against intravenous injections of serum for children.

Herrick[3] has reported particularly good results from treatment by

[1] Jour. Exper. Med., 1917, **25**, 499 and 525.
[2] Jour. Am. Med. Assn., 1921, **76**, 36.
[3] Ibid., 1918, **71**, 612.

intravenous injections of serum in severe adult cases, the patients often coming out of coma with rapid recession of the rash and symptoms. The mortality was reduced from 64 to 19 per cent. Out of Herrick's 265 cases, 64, or 26 per cent, proved fatal, but out of 137 cases given ordinary intraspinal injections and less than 45 cc. of serum ntravenously, 47, or 34 per cent, proved fatal, whereas out of 128 cases treated intraspinally with small doses and intravenously with large doses of serum, 19, or 15 per cent, proved fatal.

Of the two forms of serum therapy, intraspinal and intravenous, the former is the more important. Acute primary meningococcus bacteriemia without involvement of the meninges is rare, but when meningococci are found in the blood, serum should be given intravenously. In severe adult cases seen within the first three days serum may be given intravenously as a routine; at least one dose of 50 to 100 cc. may be given.

Repeating Doses of Serum.—It is the general rule to give an intraspinal injection of serum every day for four days; then on alternate days until the acute symptoms have subsided, and to resume the treatment if an exacerbation or a relapse occurs. In severe fulminant infections, and especially if the exudate is thick and only small amounts of serum can be introduced under pressure, it is well to repeat the injection every twelve hours until several doses have been given. Some cases require daily consecutive injections for six or more days; the average case will require from 4 to 6 injections if the treatment is begun during the acute stage; in the subacute and chronic cases many more treatments are required. There are two main indications and guides:

1. The condition of the cerebrospinal fluid.
2. The clinical condition of the patient.

In most instances the cerebrospinal fluid tends to clear up macroscopically as the disease improves. This is, however, occasionally misleading, as the fluid may become more turbid as the result of an *aseptic meningitis* or excitation of a polymorphonuclear leukocytosis due to the serum, while, in reality, the numbers of meningococcoci are diminishing and the patient is improving.

More accurate information is obtained by the microscopic examination of a stained smear of the sediment of the cerebrospinal fluid withdrawn. In fresh acute cases the cocci are numerous and mostly extracellular; improvement is indicated by a diminution in their number, and by the fact that they are mostly intracellular. We generally determine the *phagocytic index* or the relative proportion of leukocytes that have engulfed cocci and the *opsonic index* or the relative number of cocci per leukocyte as determined by counting a large number. When many cocci are present, or if they are few in number but mostly extracellular, the indications are to puncture next day, even if the clinical condition of the patient is good and the temperature is lower. The number and position of cocci are, therefore, of more

importance as a guide to subsequent injections than is the total number of pus cells.

As an indication for repeating the doses of serum the clinical condition is of most value when combined with the examination of the cerebrospinal fluid. Occasionally the patient's condition may seem to improve, although the fluid may show numerous cocci, which will subsequently aggravate the clinical condition unless the serum is administered. In favorable cases there is usually a lower temperature the day following an injection, and frequently delirium becomes less marked and there is some return to consciousness. The complexion, which is often cyanosed at first, regains a healthy color; the pain in the head, neck and limbs becomes less severe, although the neck and spine may remain stiff for several days. Finally the mind becomes clear and the patient is cheerful, and no longer irritable, apathetic and hypersensitive. He feels better and his appetite returns. When this favorable outcome supervenes the serum injections may be discontinued, to be resumed, however, upon the first evidence of a relapse. The physician should be on his guard for the appearance of acute hydrocephalus, which condition is relieved by repeated lumbar punctures.

The Serum Treatment of Cases With Thick Plastic Exudate and Subarachnoid Block.—In very severe cases the exudate may be so thick that it will not flow from the needle. In these cases the serum should be injected in small doses under pressure and the injections repeated every eight to twelve hours. As they are likely in any case to terminate fatally, the physician is justified in taking the risk of increasing intracranial pressure. It may be well carefully to inject a small amount of warm sterile salt solution, which will dilute the exudate and possibly start a flow; or a second needle may be inserted higher up, when a thinner exudate is found, or washing may be possible by injecting salt solution in the upper needle and draining through the lower.

Peet[1] has especially recommended cisternal injections of serum in cases of this kind and, indeed, in all not showing satisfactory progress because in his opinion the serum better reaches the basilar cisterna and cerebral subarachnoid spaces in greater concentration and block of the spinal subarachnoid space prevented.

In cases of spinal block the injection of serum by this route and by ventricular puncture is imperative, and McLean and Caffey[2] have recently reported the complete recovery of 8 cases by these routes of injection.

The Serum Treatment of Cases With a Dry Canal and Cases of Posterior Basal Meningitis.—Occasionally a patient improves clinically and the amount of cerebrospinal fluid becomes very scanty, the spinal tap being dry, although it is certain that the needle has entered

[1] Jour. Am. Med. Assn., 1926, **86**, 1818.
[2] Ibid., **87**, 91.

the subarachnoid space. In such instances a small amount of serum may be injected, or the injection may be dispensed with if the clinical condition continues to improve. If, however, cases with dry canals present evidences of toxemia and general aggravation of symptoms, small doses of serum should be injected under pressure and the injections repeated as often as necessary. The physician must be very cautious, however, for if there are clinical evidences of severe intracranial pressure, it is probable that there is an encapsulation of fluid within the ventricles, and shutting off of the communication between the ventricles and the subarachnoid space. In this *posterior basic meningitis* intraspinal injections are dangerous and aggravate the process. In infants it is necessary to puncture the ventricles through the anterior fontanel as first practised by Cushing and Sladen,[1] and in older children and adults by trephining at Kocher's point, removing the fluid, and if it is found to be cloudy or purulent, injecting serum. It may be necessary to tap both ventricles alternately at intervals of several days, depending upon the reaccumulation of fluid and pressure symptoms. Permanent drainage may be instituted in severe cases by means of small catheters. While the operation is not usually dangerous, the ultimate prognosis is very unfavorable.

In adults trephining and injecting serum into the ventricles has yielded, according to Marcland,[2] 4 cures among 18 cases. Landry and Hamley[3] had 1 cure out of 5 cases, but Fairley and Stewart lost all of 9 cases. In place of trephining and injecting the serum Herrick recommends Cobb's method of breaking down adhesions around the foramen magnum and fourth ventricle by manipulations of the head under general anesthesia to relax the neck muscles. This method may produce an increased flow of spinal fluid.

Cisternal puncture and injection of serum may also be tried. Ayer has conducted the puncture in 20 cases without mishap. Mitchell and Reilly[4] have recorded the recovery of an infant, aged four months, following repeated cisternal punctures and drainage and the injection of 5 to 8 cc. of serum each time.

As previously stated, Peet and McLean and Caffey have recently reported very favorably upon cisternal injections or combined cisternal and ventricular injections in the treatment of these otherwise generally hopeless and fatal cases.

The Serum Treatment of Subacute and Chronic Meningitis.—If there is no evidence of sepsis, if the mind is clear and the neck limber, if the general conditions are good and the cerebrospinal fluid is practically cleared up, the affection is most likely hydrocephalitic, and may be relieved by repeated spinal punctures, with removal of as much fluid as is safe, using blood-pressure as an index. If meningococci are

[1] Jour. Exper. Med., 1908, **10**, 548.
[2] Bull. et mém. Soc. d. hôp., 1918, **42**, 1218.
[3] Am. Jour. Med. Sci., 1919, **157**, 210.
[4] Ibid., 1922, **164**, 66.

present in cultures of the fluid small amounts of serum may be injected. The prognosis in these cases, however, is generally bad, as the process is prolonged and the patient finally succumbs.

In the second form of chronic meningitis, when the meningeal symptoms are active, intensified, and persistent, serum should be administered every few days in the same manner and in the same dosage as in the acute cases. Improvement is, however, usually temporary, and the ultimate prognosis is very grave.

Serum Sickness.—Intraspinal injections of serum result in the sensitization of the patient in just the same manner as if serum were injected by other routes. The percentage of cases developing serum sickness is likely to be high, since antimeningitis serum is not refined (Sophian reports 60 per cent of his cases as developing the condition), and while the symptoms are distressing, they are seldom alarming, and fatal anaphylaxis is extremely rare. Occasionally the onset of serum sickness may be mistaken for a recurrence of meningitis, but if the meningeal condition has been responding as well as could be expected, it is wise to let the patient alone, rather than to make additional punctures and cause further depression. Local sedatives, laxatives, atropine, sedatives and, at times, morphine, are indicated. (See page 770.)

Summary and General Plan for Serum Treatment of Meningococcus Meningitis.—For cases of average severity first diagnosed on or about the third day of the disease the following plan of serum treatment is advised: Spinal fluid should always be drained off, in amounts slightly more than the amount of serum injected. If the spinal fluid pressure is high it is well to drain spinal fluid until it flows at the rate of about 1 drop in five seconds. *Each spinal fluid should be examined for meningococci.*

First Day.—For children under twelve years of age: 15 cc. of serum intraspinally at the time of first spinal puncture or as soon as possible thereafter. Repeat the drainage and injection of serum eight to twelve hours later.

For children over twelve years of age and adults: 20 to 30 cc. of serum intraspinally as soon as possible. Blood culture. Severe cases in adults to receive 100 to 150 cc. serum intravenously one hour after the subcutaneous injection of 1 cc. of the serum for desensitization. Intraspinal injection to be repeated eight to twelve hours later.

Second Day.—Repeat the intraspinal injection. If very severe give a second intraspinal injection eight to twelve hours later. If blood culture is positive give a second intravenous injection of serum.

Third and Fourth Days.—One intraspinal injection of serum. If patient is not improving or growing worse give a second injection on these days about eight to twelve hours later.

Fifth Day.—If spinal fluid removed in fourth day shows no meningococci, spinal puncture may be done and fluid removed if it is under

pressure, but serum may be omitted. As a general rule, however, it is well to inject serum intraspinally.

The appearance of the fluid if cloudy may be misleading because leukocytes may be present by reason of irritation of the meninges by the serum and meningococci absent.

Serum should be injected intraspinally at least once a day until two successive spinal fluids have proved sterile. At that time serum may be stopped, but a sharp watch kept up for relapses. Serum sickness will probably develop and should not be mistaken for a relapse.

Treatment of Meningitis With Human Serum.—MacKenzie and Marin,[1] in 1908, treated 16 acute cases with intraspinal injections of 15 to 20 cc. of fresh sterile human serum, with mortality of 38 per cent.

Cases of meningitis have also been treated with intraspinal injections of serum from convalescent cases of the disease as well as by injections of the patient's own serum.

Convalescent serum may doubtless prove worth administering in exceptional cases, if derived from an individual recovered from the same type of infection, but the curative value of normal human serum is questionable, although its addition to antimeningococcus serum may prove distinctly worth while in the treatment of some cases, as previously discussed, by increasing the opsonic and bactericidal activity of the latter.

Vaccine Treatment of Meningococcus Meningitis.—Vaccines have been advocated in the treatment of subacute and chronic cases when serum appears to be losing its effect. Rolleston[2] reports the treatment of 21 cases with vaccines, always in addition to other treatment, with a mortality of 23.5 per cent.

Crowe[3] considered autogenous vaccines of aid in treatment and began early in the acute stage with small doses of 1,000,000 cocci. Hall,[4] Collins,[5] Sophian,[6] Colebrook,[7] Fairley and Stewart,[8] Worster-Drought and Kennedy,[9] Chalmers and O'Farrel,[10] MacLagan,[11] and others have also reported favorably upon the use of vaccines in subacute and chronic cases of the disease.

The vaccines should be autogenous; if a stock vaccine is used it should be polyvalent in order to make sure that it includes the type producing the disease. In subacute and chronic cases the vaccine may contain 1,000,000,000 cocci per cubic centimeter. Subcutaneous injections may be given every five days beginning with 0.1 cc. for persons fifteen years of age or older and gradually increasing until 1 cc. is being given at one time.

[1] Jour. Path. and Bacteriol., 1908, **12**, 539.
[2] Lancet, 1919, i, 645.
[3] Lancet, 1915, i, 1127.
[4] Medical Research Committee Report, 1916.
[5] British Med. Jour., 1915, i, 287.
[6] Epidemic Cerebrospinal Meningitis, St. Louis, C. V. Mosby Company, 1913, p. 192.
[7] Lancet, 1915, i, 1026.
[8] Commonwealth of Australia Service Publication, 1916, No. 9.
[9] Cerebrospinal Fever, London, A. and C. Black, 1919, p. 428.
[10] Jour. Trop. Med. and Hyg., 1915, 1916, pp. 40 and 101.
[11] Edinburgh Med. Jour., 1918, **20**, 375.

THE GENERAL TREATMENT OF CEREBROSPINAL MENINGITIS.

The patient should be *isolated* and as a general rule treatment is better conducted in a hospital.

Even mild cases should be kept in bed for at least three weeks.

Good nursing is essential. The position of the patient should be changed at intervals and great care taken of the skin to prevent the development of bed-sores. The mouth should be cleansed at frequent intervals and likewise the eyes if inflamed. It is well to clip the hair short.

Retention of urine will require catheterization with rigid aseptic precautions.

The *bowels* should be evacuated daily.

The *diet* should be liquid or soft and as generous as possible in view of the rapid wasting of the disease.

Headache is best relieved by spinal drainage as is likewise true of vomiting. An ice-bag may be applied to the head. Phenacetin may be tried.

Insomnia may require sulphonol (20 to 30 gr. for adults), veronal or chloral hydrate with potassium bromide. Morphine is sometimes required and should be given without hesitation to afford relief from pain and to produce sleep. Hyoscine is sometimes combined with it to advantage in maniacal cases.

Hot applications are often times useful for the relief of *backache*.

Digitalis may be required for the *heart* and circulation.

Complications must be treated as they arise. Ventricular drainage is required in well-marked internal hydrocephalus.

Helmitol (hexamethylentetramine anhydromethylene citrate) is said to liberate formaldehyde in an alkaline as well as in acid media, and while it possesses some bactericidal effects upon meningococci *in vitro*, yet it would appear impossible to administer sufficient by intravenous injection (60 gr.) or by intrathecal injection (10 to 30 gr. in an ounce of saline or horse serum) materially to influence meningococcus meningitis or to detect free formaldehyde in the urine or cerebrospinal fluid.

A variety of chemical agents like lysol, phenol, protargol and eusol have been injected intrathecally, but likewise without beneficial results; indeed, these substances may prove distinctly harmful. Thus, Flexner and Amoss have found lysol and protargol harmful in experimental meningococcus infections of guinea-pigs and monkeys on account of their antileukotatic and antiphagocytic properties and, since recovery from all forms of meningitis is largely due to phagocytosis, it is very important that nothing is injected capable of paralyzing this important process.

On the other hand, however, the oral administration of helmitol in dose of 15 gr. every twenty-four hours is said to keep the cerebrospinal fluid under its influence, and its administration may be helpful in the treatment of those fulminant and apparently serum-resistant cases

of meningococcus meningitis occasionally encountered. Furthermore the intraspinal injection of neutral acriflavine in dose of 0.0001 gm. per kilogram (0.1 cc. of 1 to 1000 per kilogram) mixed with the serum may be worth trying, although in a few cases in which this compound has been injected the results have not been encouraging.

THE TREATMENT OF CARRIERS.

The treatment of carriers is very unsatisfactory despite the use of a great number of different antiseptics in sprays, nasal douches and gargles. The naso-pharynx is the area of particular importance. Probably plenty of out-door air and sunshine are as good as anything. Vaccines are of no value; neither is the injection of serum.

Sophian has advocated the use of 0.5 per cent hydrogen peroxide as a nasal spray and gargle.

Foster and Gaskell have used potassium permanganate (1 to 1000) in solution with 1.5 per cent sodium sulphate.

Worster-Drought and Kennedy have found 1 per cent solutions of chloramine-T as a nasal douche of definite value if personally supervised by the physician.

Küster has tried treatment in an inhaling chamber with chlorine liberated from hypochorite in contact with acids.

Cultures should not be taken until at least forty-eight hours have elapsed since the last local treatment. If negative a second culture should be made several days later. If this is negative the patient or carrier may be discharged.

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